Long-Term Survival After Salvage Thoracic Surgery on a Patient with ALK-Rearranged Metastatic Lung Adenocarcinoma After Progression on Targeted Therapy

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Abstract: Targeted therapy for patients with advanced non-small cell lung cancer (NSCLC) is often challenged by the arising of drug resistance. After progression to targeted therapy, treatment options include continued targeted therapy, definitive local therapy, and the combination of both. While there is evidence that local ablative radiotherapy may prolong the disease control by targeted therapy, little is known regarding the relevance of salvage thoracic surgery in this setting. Herein, we presented a case of stage IV lung adenocarcinoma with concurrent EML4-ALK and TAC1-ALK fusion who had long-term survival after salvage thoracic surgery. The patient underwent a multidisciplinary treatment scheme that consisted of radiotherapy, ALK inhibitor crizotinib, and surgery, with blood-based genomic profiling for monitoring disease progression. Notably, salvage thoracic surgery was performed after progression on the crizotinib therapy and acquired ALK F1174C mutation was identified, which has been shown to be resistant to crizotinib and possibly sensitive to ceritinib. The patient benefited from salvage thoracic surgery with a remarkable progression-free survival of 31 months at last follow-up, and the patient maintained high-performance status throughout the course of management. To the best of our knowledge, this is the first case reporting on the long-term survival outcome from salvage thoracic surgery after crizotinib treatment in an NSCLC patient carrying double ALK fusion.

Keywords: advanced non-small cell lung cancer, multidisciplinary treatment, salvage thoracic surgery, crizotinib, ALK F1174C mutation

Introduction
Non-small cell lung cancer (NSCLC) makes up nearly 85% of lung cancer cases and is one of the most lethal forms of malignancies. Surgery is currently the cornerstone of NSCLC treatment since it provides an opportunity for cure. Unfortunately, more than 70% of patients are diagnosed with advanced NSCLC (stage III and IV) at diagnosis. The standard-of-care consists largely of systemic treatment modalities, such as concomitant chemo- and radiotherapy for the majority of patients in stage III, and targeted therapy, chemotherapy, immunotherapy, or chemo-immunotherapy for stage IV patients and some stage III NSCLC patients. However, salvage thoracic surgery may still be a viable option for advanced NSCLC (aNSCLC) beyond frontline treatment, as the disease progression as a result of drug resistance. Salvage surgery of lung tumors refers to the resection of residual or recurrent tumors or in urgencies...
such as severe infections. There is evidence that tumor excision, indicated by disease downstaging to resectable tumor or improved performance status after targeted therapy, may be safe and beneficial. However, in the setting of progression on targeted therapy, although definitive local therapies, such as local ablative radiotherapy and surgery, are recommended for subsequent treatment, the role of salvage thoracic surgery is poorly characterized. A recent retrospective analysis of the relevance of surgical resection after treatment with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) inhibitors reported a median recurrence-free survival of 15 months after salvage thoracic surgery. However, the majority of patients (33/36) harbored EGFR alterations, and few (3/36) patients carried ALK fusions in this previous study. Therefore, there is a dearth of evidence in assessing the safety and efficacy of salvage thoracic surgery in ALK-altered, progressive aNSCLC. Herein, we described the multidisciplinary treatment and outcome of a stage IV lung adenocarcinoma patient harboring double ALK fusion. Surgery was performed to remove the enlarged primary lung tumor after second-line therapy with crizotinib. At the time of manuscript preparation, the patient had no evidence of recurrence or progression with a progression-free survival (PFS) of 31 months.

Case Presentation
A 55-year-old woman was referred to our hospital in Nov 2016 with a two-month history of left-sided hip pain. Chest computed tomography (CT) noted a mass in the left lower pulmonary lobe (6.0 cm, Figure 1A). Pelvic CT revealed a soft tissue mass with bone destruction, which suggested a neoplastic lesion in the left-hip joint (Figure 1D and G). A needle biopsy of the primary lung tumor was conducted, and a pathologic review led to a diagnosis of stage IV lung adenocarcinoma (T2aNxM1b). As there was insufficient material for mutational profiling of the lung biopsy, next-generation sequencing (NGS) with a panel of 168 lung cancer-related genes (Burning Rock Biotech, Guangzhou, China) was performed with plasma and identified two ALK fusions, EML4-ALK (E6:A20) fusion with a mutational allele frequency (AF) of 5.47% and TAC1-ALK (Tintergenic: A20) fusion with an AF of 5.27%. The patient was then started on a combination of crizotinib, zoledronic acid, and bevacizumab based on the following reasons. First, the time of progression on first-line treatment (Jan 2018), no standard-of-care was recommended in guidelines of Chinese Society of Clinical Oncology (CSCO, http://www.cSCO.org.cn/cn/index.aspx) for the treatment of patients with ALK-rearranged metastatic NSCLC who were previously treated with crizotinib and data on the efficacy of novel ALK-tyrosine kinase inhibitors (TKIs) in a randomized clinical trial is lack. Second, it has been documented that patient with advanced ALK-rearranged NSCLC after initial disease progression could obtain benefit from continued crizotinib. Third, several clinical trial studies have demonstrated that bevacizumab, as a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF), is safe, feasible, and effective as frontline treatment of advanced NSCLC. Given the local progression after treatment of crizotinib and radiotherapy plus zoledronic acid, crizotinib beyond progression combined with bevacizumab and zoledronic acid were given to the patient between Jan 2018 and Jul 2018. Positron emission tomography (PET)-CT scans in Apr 2018 revealed increased metabolic activity in both the primary lung tumor (Figure 1H) and metastatic lesion to the left-hip joint (Figure 1I).

Despite the initial partial response, the disease progressed six months later, when CT scans showed an enlarged primary lung tumor (Figure 1B) while the hip joint metastasis remained stable (Figure 1C). After multidisciplinary consultation and preoperative evaluation, the patient was evaluated at an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 and deemed eligible for surgery. Video-assisted thoracoscopic left lower lobectomy and systematic nodal dissection were performed. Gross total resection of the primary lung tumor with a diameter of 2.9 × 3.6 cm was achieved. Pathologic review of surgical specimens revealed a left lung adenocarcinoma with no necrosis, metastases to the 7th and 11th group of lymph nodes, and no metastases to the 6th, 9th and 10th group of lymph nodes. NGS profiling of the primary lung tumor with a panel of 520 cancer-related genes (Burning
Figure 1 PET-CT/CT scans of the primary lung tumor and hip bone lesion. Chest CT scans of the primary lung tumor prior to first-line treatment (A), after first-line treatment (B), and after second-line treatment (C); Pelvis CT scans of the hip bone lesion prior to first-line treatment (D and G), after first-line treatment (E), and after second-line treatment (F); PET-CT scans of the primary lung tumor in Apr 2018 (H) and Jan 2020 (J); PET-CT scans of the metastatic lesion to left hip joint in Apr 2018 (I) and Jan 2020 (K). Red arrows indicated the primary lung tumors and blue arrows indicated the hip bone lesions.

Abbreviation: PET-CT, positron emission tomography-computerized tomography.

Figure 2 Diagram presentation of multimodal treatment described in this report. The patient underwent three lines of therapies that consisted of radiotherapy, ALK inhibitor crizotinib, and surgery, with molecular monitoring. Notably, salvage thoracic surgery was performed after progression on second-line treatment based on crizotinib and was followed by a remarkable PFS of 31 months at last follow-up.

Abbreviations: ctDNA, circulating tumor DNA; PR, partial response; PFS, progression-free survival; SD, stable disease.
Rock Biotech, Guangzhou, China) revealed three clonal alterations: ALK F1174C with an AF of 9.39%, EML4-ALK fusion with an AF of 16.05%, and TAC1-ALK (Tintergenic: A20) fusion with an AF of 15.51%. Crizotinib was continued after the surgery. As of the follow-up in Jan 2020, there was no sign of recurrent disease in the lung (Figure 1K), and the bone metastasis remained stable (Figure 1K). The patient was in high-performance status (ECOG PS of 1). She had therefore achieved an overall survival of 51 months, including a noteworthy 31-month PFS after salvage thoracic surgery (Figure 2).

Discussion

In this report, we presented a case of successful salvage thoracic surgery following progression on targeted therapy in a metastatic, ALK-rearranged lung adenocarcinoma patient. The role of salvage thoracic surgery in treating aNSCLC has not been well characterized. In the selected advanced EGFR-mutant NSCLC patients who received EGFR inhibitor gefitinib and then achieved a resectable disease, removal of residual disease was associated with a median overall survival of 31 months, but recurrence-free survival after surgery was unsatisfactory. For patients progressing on targeted therapy, local treatment modalities are recommended. Although local ablative therapy has been shown to prolong the duration of disease control when combined with continuation of the EGFR- or ALK-TKIs (median PFS of six months), little is known regarding the safety and benefit of surgical resection in this setting. Our case therefore provides valuable evidence that salvage thoracic surgery after progression on ALK-TKIs may lead to favorable survival outcomes.

Although ALK rearrangements have been reported in 5% to 6% of NSCLC patients, more than 30 types of ALK fusion partners (such as EML4, KIF5B, and KLC1) have been identified in NSCLC to date. Double ALK fusion is a very rare event in ALK-rearranged NSCLCs. To the best of our knowledge, only a few of cases have been documented in the literature, which reveal that patients with NSCLC who harbor double ALK fusion (such as NLRC4-ALK and EML4-ALK, CDK15-ALK and EML4-ALK, CCNY-ALK and ATIC-ALK, PRKCB-ALK and EML4-ALK, BCL11A-ALK and EML4-ALK) could benefit from ALK-TKI crizotinib. In the present work, the patient is the first reported case that harbors concurrent TAC1-ALK (Tintergenic: A20) and EML4-ALK fusion. We also found that this patient achieved durable response to crizotinib plus radiotherapy with a PFS of 14 months. Our findings provide important information for future treatment decision-making in patients with double ALK fusion.

Moreover, compared with other local treatment options, surgery offers a unique advantage as it could enable genomic profiling of the tumor tissue and therefore guiding treatment options. Dynamic surveillance with NGS is routinely performed with blood for most aNSCLC patients on targeted therapy, and in the usual case when neoplasms driven by TKI-resistant mutations emerge and eventually manifest as progressive disease, these mutations are more likely to be identified with tissue-based testing. This advantage is illustrated in our case, in which all three surgical specimens were found to harbor an additional ALK F1174C, a mutation known to render resistance to crizotinib and perhaps sensitive to ceritinib based upon structural insights and sporadic reports. An in silico study has revealed the allosteric effect of F1174C resistance mutation on ceritinib in ALK. An in vitro study has demonstrated that ALK F1174C is resistant to crizotinib and sensitive to ceritinib, alectinib, brigatinib, and lolaatinib. In addition, alectinib, brigatinib, and lolaatinib have been approved for the treatment of patients with metastatic ALK-positive NSCLC. These findings suggest that patients harboring ALK F1174C might benefit from alectinib, brigatinib or lolatinib. Clinical trials are needed to explore the efficacies of these three ALK-TKIs in metastatic ALK-rearranged NSCLC patients who acquired resistance mutation ALK F1174C after crizotinib treatment.

In summary, we described the successful multimodal treatment of a metastatic lung adenocarcinoma patient carrying double ALK fusion at diagnosis. The course of management spanned over 51 months, consisting of three lines of therapies that comprised targeted therapy and salvage thoracic surgery. Notably, the excision of the residual lung tumor was followed by a PFS of 31 months. To the best of our knowledge, this is the first case report on the long-term survival outcome after salvage thoracic surgery as a later-line treatment for advanced NSCLC patients with double ALK fusion.

Ethics Statement

This study was approved by the Ethics Committee of Shenzhen People’s Hospital. Patient provided informed consent to the study and permitted the use of tumor tissue. Written informed consent was obtained from the patient for publication of this case report. An institutional approval has been obtained to publish the case details.
Disclosure
The authors report no conflicts of interest in this work.

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