Long-term complete response in a patient with postoperative recurrent ALK-rearranged lung adenocarcinoma treated with crizotinib: A case report

TAKAYUKI KOSAKA1, TOSHIKI YAJIMA1, EI YAMAKI1, SESHIRU NAKAZAWA1, KENJI TOMIZAWA1, RYOICHI ONOZATO1, AYAKO YAMAZAKI2, JUNKO HIRATO2, YASUSHI YATABE3, KIMIHIRO SHIMIZU1, AKIRA MOGI1 and KEN SHIRABE1

1Department of General Surgical Science, Graduate School of Medicine, Gunma University; 2Department of Pathology, Gunma University Hospital, Maebashi, Gunma 371-8511; 3Department of Pathology and Molecular Diagnostics, Aichi Cancer Center, Nagoya, Aichi 464-8681, Japan

Received February 18, 2019; Accepted June 10, 2019

DOI: 10.3892/mco.2019.1892

Abstract. Anaplastic lymphoma kinase (ALK) gene rearrangements are found in approximately 5% of non-small cell lung cancer (NSCLC) patients, and are enriched in patients with adenocarcinoma histology, patients with tumors of young onset, and never or light-smokers (1,2). Several ALK tyrosine kinase inhibitors (TKIs), such as crizotinib, alectinib, ceritinib, brigatinib, and lorlatinib have been developed for ALK-positive NSCLC (3-7), and crizotinib was the first multi-targeted ALK-TKI to be approved. Despite initial dramatic responses to crizotinib, the majority of patients show relapse within 12 months because of the development of resistance (3). Only a few cases have shown long-lasting response to crizotinib, especially over 5 years. Here we experienced a very rare case of ALK-positive lung adenocarcinoma with postoperative recurrence that maintained complete response with crizotinib for over 5 years.

Case report

A 60-year-old male smoker with a right upper lobe lung tumor was referred to our hospital for operation (Fig. 1A). The patient had a medical history of controlled hypertension and hyperlipidemia. Transbronchial biopsy showed histology of adenocarcinoma. Radical right upper lobectomy with mediastinal lymph node dissection was performed. Pathological examination revealed moderately differentiated adenocarcinoma with acinar and solid component with cribriform pattern (Fig. 1B-D). Micropapillary component was identified within the acinar component and signet-ring cells were present in the solid component. The tumor was 7-cm in diameter and pleural invasion to superficial pleural connective tissue, vessel invasion, and lymphatic invasion were detected. Metastasis to hilar node was present, and the final pathological stage was IIB according to the 7th edition of tumor, node, and metastasis (TNM) classification. As postoperative adjuvant therapy, the patient was administered three cycles of carboplatin and S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) followed by one year of tegafur-uracil (UFT; Taiho Pharmaceutical). One year after the operation, multiple small nodules were detected by computed tomography (CT) and follow-up CT scan showed that nodules continued to grow (Fig. 2A). At one year and 8 months after the operation, thoracoscopic resection of a nodule in the right lower lobe was performed for pathological diagnosis. Pathological examination of the lung nodule revealed identical histology as the initial surgical specimen (i.e., adenocarcinoma with solid tumor with acinar...
and micropapillary components). Lung cancer recurrence was diagnosed, and all other nodules detected by CT were also considered to be recurrent lesions. Magnetic resonance imaging of brain and 18F-fluorodeoxyglucose positron emission tomography revealed there was no other metastasis than multiple lung metastases. Immunohistochemical analysis of the initial surgical specimen using a commercial assay showed that tumor cells were positive for ALK and fluorescence in situ hybridization confirmed the presence of ALK gene rearrangement with a positive cell rate of 62%. Analysis of the initial surgical specimen by next-generation sequencing assay using FusionPlex (Archer, Boulder, CO, US) revealed a variant type 2 of *echinoderm microtubule-associated protein-like 4 (EML4)-ALK* rearrangement [exon 20 of *EML4* fused to exon 20 of *ALK* (E20;A20)].

As the first-line treatment, crizotinib was administered twice daily (250 mg) and the size of multiple nodules remarkably decreased on follow-up CT after a month. Complete response was confirmed after 4 months (Fig. 2B) and was maintained over 5 years after the first administration of crizotinib. Grade 1 photopsia and diarrhea were the only adverse events observed.
Discussion

We present here a case of ALK-rearranged lung adenocarcinoma with postoperative multiple pulmonary metastases that showed complete response to crizotinib over a period of 5 years. The majority of patients treated with crizotinib have a relapse within 1 year (3). Clinical trials of crizotinib revealed that progression-free survival (PFS) was 10.9 months after first line treatment (3) and 7.7 months in patients who had received one prior platinum-based regimen (8). Rangachari et al (9), reported two cases of advanced lung adenocarcinoma with a PFS exceeding 5 years with crizotinib as first-line treatment. To the best of our knowledge, the current case is the third reported case of long-lasting PFS by crizotinib treatment exceeding 5 years. In addition, the current case is the first case depicting long-term complete response to crizotinib after postoperative recurrence. The previous report by Rangachari et al (9), does not include clinical and pathological details of the two cases with long-lasting PFS, and thus it is difficult to discuss the clinicopathological tendencies of these cases.

Several variants of the EML4-ALK fusion have been previously reported (10-12). The most frequent variants are variant 1 (33%), in which exon 13 of EML4 is fused to exon 20 of ALK (E13;A20); variant 3a/b (29%), in which exon 6a or 6b of EML4 is fused to exon 20 of ALK (E6a/b;A20); and variant 2 (9%), in which exon 20 of EML4 is fused to exon 20 of ALK (E20;A20) (11). Other minor variants have also been reported. Recent studies have suggested that the response to crizotinib differs according to the ALK rearrangement variant (13-18) (Table I). Li et al (13), reported that patients with variant 2 had a longer PFS compared with patients with other variants. These clinical results are supported by in vitro studies in which Ba/F3 cells expressing variant 2 had higher sensitivity to crizotinib compared with cells expressing other variants (15,19). The results of these studies are consistent with our case, since our patient also had variant 2 fusion and achieved long PFS with crizotinib. However, such clinical differences in response or PFS vary amongst reports (13-18). Because the previous clinical studies were performed in small cohorts (Table I), a definitive conclusion has not yet been established.

In conclusion, here we presented a very rare case of variant type 2 ALK-rearranged lung adenocarcinoma that maintained complete response with crizotinib over 5 years. The efficacy of crizotinib may vary among ALK fusion variants, indicating that ALK variant type may represent an important factor in guiding the treatment strategy for ALK-rearranged lung adenocarcinoma. A large cohort analysis is required for further study.

<table>
<thead>
<tr>
<th>First author</th>
<th>Case</th>
<th>ORR</th>
<th>PFS Case</th>
<th>ORR</th>
<th>PFS Case</th>
<th>ORR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lei et al (18)</td>
<td>61</td>
<td>22</td>
<td>73%</td>
<td>110</td>
<td>non-v1/v3a/b; n=21</td>
<td>ORR 81%, PFS 7.4 m</td>
<td>18</td>
</tr>
<tr>
<td>Cha et al (17)</td>
<td>32</td>
<td>10</td>
<td>30%</td>
<td>x</td>
<td>100%</td>
<td>x</td>
<td>2</td>
</tr>
<tr>
<td>Yoshida et al (16)</td>
<td>35</td>
<td>19</td>
<td>74%</td>
<td>11.0 m</td>
<td>non-v1; n=16</td>
<td>ORR 63%, PFS 4.2 m</td>
<td>x</td>
</tr>
<tr>
<td>Woo et al (15)</td>
<td>51</td>
<td>13</td>
<td>44%</td>
<td>10.7 m</td>
<td>non-v3a/b; n=24, ORR 63%, 2-year PFSR 76%</td>
<td>20</td>
<td>6%</td>
</tr>
<tr>
<td>McLeer-Florin et al (14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al (13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table I. Different of efficacy of crizotinib among ALK fusion variants.

<table>
<thead>
<tr>
<th>Variant 1</th>
<th>ORR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>2-year PFSR 60%</td>
<td>20</td>
</tr>
<tr>
<td>74%</td>
<td>18.5 m</td>
<td>67%</td>
</tr>
<tr>
<td>73%</td>
<td>11.0 m</td>
<td>56%</td>
</tr>
<tr>
<td>30%</td>
<td>7.4 m</td>
<td></td>
</tr>
</tbody>
</table>

Including several types of variant ORR, overall response rate; PFS, progression-free survival; PFSR, progression-free survival rate; m, months; d, days; n, number; x, data not shown.
Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contribution

TK designed the study. TK, TY, EY, SN, KiS, KT, RO, AM, KeS wrote the manuscript. KT, TY, EY, SN, KT, RO, KiS, AM, and KeS have contributed to the clinical management of the patient. AY and JH analyzed pathological findings. YY performed the next-generation sequencing assay. All authors critically reviewed the manuscript and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval for this study was obtained from Gunma University Hospital Ethics Committee. The patient provided written informed consent. Written informed consent was obtained from the patient. Ethics approval and consent to participate

Patient consent for publication

Written informed consent was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

References