CASE REPORT

Combined small cell lung carcinoma harboring ALK rearrangement: A case report and literature review

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Keywords
Alectinib; ALK; combined small cell carcinoma; immunochemotherapy; literature review.

Abstract
Combined small cell lung cancer (c-SCLC) is a relatively rare subtype of SCLC and is defined by the combination of SCLC and any elements of non-small cell carcinoma (NSCLC). Standard chemotherapy for patients with c-SCLC has not yet been established. Gene mutations such as epidermal growth factor receptor (EGFR) mutations may be detected in patients with c-SCLC. However, little is known about anaplastic lymphoma kinase (ALK) rearrangement in c-SCLC patients. Here, we report a young female patient who was successfully treated with alectinib for ALK-positive c-SCLC after failure of immunochemotherapy for SCLC and cytotoxic chemotherapy for adenocarcinoma. Moreover, we performed a literature review of EGFR- or ALK-positive c-SCLC patients. Our report suggests that ALK testing may be justified in patients with SCLC that contain an adenocarcinoma component.

Key points
Significant findings of the study
• This is the first report describing the treatment course comprising immunochemotherapy and ALK-TKI in a patient with c-SCLC harboring ALK rearrangement.

What this study adds
• Our case and literature review suggest that although ALK mutation is rare in patients with c-SCLC, its identification and treatment with ALK-TKIs may contribute to clinical benefits.

Introduction
Combined small cell lung cancer (c-SCLC) is a relatively rare subtype of SCLC and is defined as SCLC combined with any elements of non-small cell carcinoma (NSCLC), such as adenocarcinoma, large cell carcinoma, and squamous cell carcinoma.1 Standard chemotherapy for patients with c-SCLC remains to be established; nevertheless, c-SCLC generally appears to be less sensitive to chemotherapy compared to SCLC.2 Only a handful of reports indicate that gene mutations, such as that of the epidermal growth factor receptor (EGFR), may be detected in patients with c-SCLC, mainly in those having the adenocarcinoma component. Moreover, little is known about the anaplastic lymphoma kinase (ALK) rearrangement in patients with c-SCLC. Here, we present a literature review and report a case of c-SCLC with adenocarcinoma harboring the ALK rearrangement who was successfully treated with alectinib.

Case report
A previously healthy 39-year-old female current-smoker of 20 cigarette packs a year presented to the medical oncology...
A patient presented to the clinic with a five-day history of dyspnea on exertion. A chest computed tomography (CT) scan showed a 2.8 cm irregular mass in the right lower lobe of the lung, as well as bilateral pleural effusion, and pericardial effusion.

A transbronchial biopsy was performed against the right lower lobe mass, and the histological findings revealed c-SCLC comprising SCLC (approximately 90%) and adenocarcinoma cells (approximately 10%) (Fig 1a,b). Thyroid transcription factor-1 (TTF-1) and Synaptophysin expression were positive in both SCLC and adenocarcinoma components. Testing for ALK rearrangement using immunohistochemistry showed strong positivity for ALK in both components.
transcription factor-1 immunohistochemistry (IHC) showed partially positive staining in the small cell component with a strongly positive adenocarcinoma component (Fig 1c,d). The small cell component was diffusely positive for synaptophysin (Fig 1e) and chromogranin A, with high Ki-67 proliferation activity (approximately 70%) as per antigen immunostaining. By contrast, the adenocarcinoma component was negative for those markers (Fig 1f), with low Ki-67 proliferation activity. Moreover, the tumor cells of both histological components were strongly positive for ALK IHC (Ventana ALK-D5F3-CDx assay) (Fig 1g,h).

ALK rearrangement was also confirmed using fluorescence in situ hybridization (FISH) (LSI Medience, Tokyo, Japan), with a rearrangement-positive cell rate of 74%. Ultimately, the tumor was diagnosed as stage IV ALK-positive c-SCLC.

Because most of the transbronchial biopsy specimens showed SCLC, the patient received carboplatin, etoposide, and atezolizumab. However, brain metastases and pleural effusion progressed after two treatment cycles. Subsequent cytological examination of the pleural effusion revealed adenocarcinoma and no SCLC characteristics. The disease progression had been thought to be due to the adenocarcinoma component, hence the patient was treated with cisplatin plus pemetrexed. However, brain metastases and pleural effusion progressed after two treatment cycles. Subsequent cytological examination of the pleural effusion revealed adenocarcinoma and no SCLC characteristics. The disease progression had been thought to be due to the adenocarcinoma component, hence the patient was treated with cisplatin plus pemetrexed. However, tumor remission was not observed after one course of chemotherapy (Fig 2a). Therefore, she was treated with alectinib, and subsequent remarkable improvement was observed one month after treatment initiation (Fig 2b). All target lesions shrunk and exhibited a partial response. Currently, the patient has been receiving alectinib treatment for five months, without disease progression or remarkable adverse events.

Discussion

In this report, we present an ALK-positive c-SCLC case successfully treated with alectinib and previous similar reports are summarized in Table 1. The tumor responded to neither a combination of atezolizumab, carboplatin, and etoposide nor cisplatin plus pemetrexed; however, subsequent treatment with alectinib elicited a rapid and remarkable response. Although neuroendocrine tumors such as SCLC are known to show false positives in ALK IHC, ALK rearrangement was confirmed by both IHC and FISH in our case. Moreover, successful treatment using an ALK tyrosine kinase inhibitor (TKI) is evidence for a true ALK-positive cancer. To the best of our knowledge, this is the first report describing the treatment course comprising immunochemotherapy and ALK-TKI in a patient with c-SCLC harboring ALK rearrangement.

Table 1 summarizes selected data from the 24 cases of c-SCLC with identified EGFR or ALK mutations. In our literature review, 19 out of 21 patients with c-SCLC harboring EGFR mutations had adenocarcinoma as a subcomponent; moreover, most patients were diagnosed through surgical resection. By contrast, only four studies reported cases harboring ALK rearrangement. Furthermore, transformation to SCLC from adenocarcinoma harboring EGFR or ALK mutations has been reported after TKI use and even without TKI use; however, cases suspected of transformation to SCLC were excluded from our literature review. It is difficult to draw definitive conclusions regarding efficacy due to the paucity of TKI-treated cases. Nevertheless, some cases respond to TKIs, suggesting that this treatment may be an option for patients with mutant c-SCLC.

Compared to SCLC, systemic chemotherapy appears to have a lower efficacy on c-SCLC; moreover, c-SCLC has a poorer prognosis, but there are conflicting reports, mainly regarding limited-stage diseases. c-SCLCs are typically treated according to SCLC regimens for extensive-stage cancer, such as platinum plus etoposide. Concerning driver mutations, the frequency of EGFR
mutations is reportedly low in SCLC (approximately 1%–5%)\textsuperscript{27}; whereas its frequency in c-SCLC is unknown, but \textit{EGFR} mutations are mainly associated with the adenocarcinoma component.\textsuperscript{3, 28} The frequency of actionable \textit{ALK} mutations (ie, excluding \textit{ALK}-IHC false positive cases) remains unknown in patients with SCLC, and there are very few previous reports regarding \textit{ALK} mutations in c-SCLC. Underestimated diagnosis in nonsurgical patients possibly blur the accurate frequency of c-SCLC. In fact, one study reported that 28\% of surgically resected SCLCs were diagnosed as c-SCLCs.\textsuperscript{29} Limited specimens such as that from cytology or a small biopsy tend to provide insufficient diagnostic information. Moreover, overlooking the adenocarcinoma component may lead to missed potential

| References | Age/ Sex | Smoking | Stage | Sample type | Histology | Mutation | Mutation type | Mutation detection | TKI use | Response |
|------------|---------|---------|-------|------------|-----------|----------|--------------|-------------------|---------|----------|
| Tatematsu et al.\textsuperscript{3} | 69/M | Yes | IA | Biopsy\textsuperscript{†} | SCLC/Ad | EGFR | L858R | Both components | NS | - |
| Siegle et al.\textsuperscript{4} | 82/M | Yes | IA | Surgical | SCLC/Ad | EGFR | Ex19del | Both components | NS | - |
| Shi et al.\textsuperscript{5} | 71/M | Yes | I\textsuperscript{†} | Surgical | SCLC/Ad | EGFR | L858R | Only Ad | NS | - |
| Lu et al.\textsuperscript{6} | 61/M | Yes | IIA | Surgical | SCLC/Sq | EGFR | Ex19del | NS | NS | - |
| Wakuda et al.\textsuperscript{7} | 73/M | Yes | IIB | Surgical | SCLC/Ad | EGFR | G719A | NS | NS | - |
| Iijima et al.\textsuperscript{8} | 63/M | Yes | IIB | Surgical | SCLC/Ad | EGFR | Ex19del | Both components | NS | - |
| Lu et al.\textsuperscript{9} | 64/F | Yes | IIIA | Surgical | SCLC/Sq | EGFR | Ex19del | Both components | NS | - |
| Norkowski et al.\textsuperscript{10} | 66/F | Yes | IIIA | Surgical | SCLC/Ad | EGFR | G719A, Ex21\textsuperscript{‡} | Both components | NS | - |
| Fukui et al.\textsuperscript{11} | 62/F | No | IIIB | Surgical | SCLC/Ad | EGFR | L858R | Both components | NS | - |
| Lin et al.\textsuperscript{12} | 66/F | Yes | IVA | Surgical | SCLC/Ad | EGFR | L858R | Both components | NS | - |
| Takagi et al.\textsuperscript{13} | 77/F | No | IVB | Surgical | SCLC/Ad | EGFR | L858R | Only Ad | Erlotinib | NS |
| Tanaka et al.\textsuperscript{14} | 67/M | No | IVB | Surgical | SCLC/Ad | EGFR | L858R | Both components | Afatinib | NS |
| Varghese et al.\textsuperscript{15} | 63/M | No | ES | NS | SCLC/Ad | EGFR | L858R | Only Ad | NS | - |
| Toyokawa et al.\textsuperscript{16} | 72/M | Yes | IB | Surgical | SCLC/Ad | EGFR | Ex19del | Only SCLC | NS | - |
| Bai et al.\textsuperscript{17} | 68/F | Yes | IIA | Surgical | SCLC/Ad | ALK | ALK rearrangement (IHC/FISH) | Both components | NS | - |
| Sim et al.\textsuperscript{18} | 64/M | Yes | IIB | Surgical | SCLC/Ad | ALK | ALK rearrangement (IHC/FISH) | Both components | Alectinib | PR |
| Present case | 39/F | Yes | IIIB | Surgical | SCLC/Ad | ALK | ALK rearrangement (IHC/FISH) | Both components | Erlotinib\textsuperscript{§} | SD |

\textsuperscript{†}Details not specified. \textsuperscript{‡}Ex21 L833_V834delinsFL. \textsuperscript{§}This patient received erlotinib in combination with carboplatin and etoposide. Ad, adenocarcinoma; DS, direct sequencing; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; NS, not specified; NSCLC, non-small cell lung cancer; PR, partial response; SCLC, small cell lung cancer; SD, stable disease; Sq, squamous cell carcinoma; TBB, transbronchial biopsy; TKI, tyrosine kinase inhibitor.
benefits from a targeted therapy. Although testing all small biopsy samples with nonadenocarcinoma histology is not recommended, expert consensus opinion in the molecular testing guidelines\(^30\) suggest that molecular biomarker testing may be used in tumors with histological types other than adenocarcinoma when clinical features indicate a high probability of a targetable mutation. Therefore, based on our case and review of the literature, performing molecular testing in patients with SCLC with an adenocarcinoma component may be reasonable, especially when the condition is accompanied by specific characteristics such as young patients (<50 years)\(^30\) and non-smokers or light smokers (<10 packs per year).\(^31\) Importantly, ALK rearrangement should be confirmed not only through IHC but also using other molecular techniques such as FISH. Ultimately, further research is needed to better understand the optimal chemotherapeutic strategy for c-SCLC.

**Disclosure**

The authors have no conflicts of interest to declare.

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