Complete tumor response in a patient with locally advanced lung large cell neuroendocrine carcinoma treated with Sintilimab plus platinum-based chemotherapy: a case report

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Case report

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Abstract

Background

pulmonary large-cell neuroendocrine carcinoma (LCNEC) is a rare subset of lung cancer with a poor prognosis. As LCNEC is an uncommon malignancy, the optimal treatment for LCNEC has not been established.

Case presentation

: we report a case of a 66-year-old man diagnosed with unresectable, locally advanced LCNEC who presented a partial radiographic response to immunotherapy combined with chemotherapy. Salvage surgery was performed after 4 cycles of docetaxel and cisplatin (DP) regimen plus sintilimab, which is a highly selective, fully human antiprogrammed death-ligand 1 monoclonal antibody. Moreover, a pathologic analysis of the resected piece revealed the absence of residual viable tumor cells.

Conclusion

this case suggests that patients with locally advanced LCNEC may benefit from neoadjuvant chemo-immunotherapy, it is worthy for further study.

1. Introduction

Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is an uncommon but destructive type of malignancy, demonstrated in a recent study to be more common among older adult males who have been smoking for decades ¹, comprising < 3% of all lung carcinoma ². Owing to its rarity, no extensive, prospective, and randomized clinical trials have been performed; choosing the optimal therapy regimen is challenging. In pathological performance, it covers the characteristics of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) ³, making the clarification of its attribution controversial. In the 2015 World Health Organization Classification of Lung Tumors, LCNEC was attributed to neuroendocrine tumor. The treatment strategy with reference to the National Comprehensive Cancer Network is based on the NSCLC project. There are no significant symptoms at the early stage; however, we detected it when it had developed to a locally advanced or advanced stage. LCNEC has a poor prognosis, with < 5% survival rates for stage IIIB–IV⁴. Surgery is still recommended, although not enough for the advanced types; therefore, neoadjuvant chemotherapy, radiotherapy, immune checkpoint inhibitors (ICIs), etc., are needed.

Herein, we report a locally advanced LCNEC with complete tumor response. The patient accepted surgery after sintilimab plus platinum-based chemotherapy. This case suggests that patients with locally advanced LCNEC may benefit from neoadjuvant chemo-immunotherapy.

2. Case Presentation

A 66-year-old man, who had a history of smoking, was admitted to our hospital with a 6-month history of cough with an Eastern Cooperative Oncology Group performance status of 1 point (ECOG 1) in June 2020. He had no significant medical history. A fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG PET-CT) revealed a $6.5 \times 7.8 \times 7.0$ -cm mass in the superior lobe of the right lung, with mediastinum invasion, right hilar lymph nodes, and mediastinal lymph node in station 4R metastases (Fig. 1). TNM classification (eighth edition) was cT4N2M0, consistent with stage cⅢB. Then, he underwent a CT-guided percutaneous transthoracic needle aspiration biopsy, suggesting a poorly differentiated LCNEC. Immunohistochemistry also showed PD-L1 expression in 10% of the cancer cells (Fig. 2), whereas no ALK or ROS-1 expression was observed. Next-generation sequencing (NGS) did not reveal any TKI-targetable mutation.

Therefore, the patient underwent a 4-cycle chemotherapy of docetaxel and cisplatin (DP) regimen combined with sintilimab (200 mg, every 3 weeks) from July 2020 to September 2020. After the treatment, chest CT scan images demonstrated a decrease in tumor size (Fig. 3). According to the guidelines of the Response Evaluation Criteria in Solid Tumors (version 1.1), the patient was considered to have a partial response.

In light of the impressive tumor response and considering the patient's young age and good ECOG performance status (ECOG 0 after the treatment), right upper lobectomy with right hilar lymph node and mediastinal lymph node dissection together with lysis of pleural adhesions were performed on October 16, 2020. A histological analysis of the resected lung and lymph nodes showed the absence of viable tumor cells (Fig. 4). Therefore, the pathological TNM classification (eighth edition) was ypT0 ypN0 (R0). Sintilimab was continued after the surgery, and an additional 4-cycle chemotherapy of the DP regimen was planned.

Figure 1. Evaluation by FDG PET-CT at diagnosis. The mass in the superior lobe of the right lung was considered as the primary tumor.

Figure 2. Pathology at the time of diagnosis. Left: hematoxylin and eosin (HE) staining shows neoplastic cells with morphological characteristics of NSCLC. Right: immunohistochemistry reveals a diffuse expression of cytokeratin, leading to the diagnosis of lung LCNEC. Picture magnification: 20×; scale bar: 50 μm.

Figure 3. CT scan showing an decreased tumor size in the right lung.

Figure 4. At the time of surgery. Left: HE staining shows a phagocytic reaction in the necrotic area of former cancer tissue, with no residual viable cancer cells. Right: HE staining displays a collagen fiber hyperplasia in the necrotic area of former cancer tissue, with no residual viable cancer cells. Picture magnification: 20×; scale bar: 50 μm. Color online.

3. Discussion

LCNEC is a pathological subtype of pulmonary neuroendocrine carcinoma, with the characteristics of high invasiveness and poor prognosis, and it is highly related to smoking ⁵. LCNEC is a type of biologically aggressive cancer that behaves similarly to small cell carcinoma ⁶. As most patients are diagnosed at the advanced stage, surgical treatment is limited, and the chances of recurrence are high. Therefore, systemic treatment is needed to improve the curative effect.

As LCNEC is an uncommon malignancy, the optimal treatment is unknown. The primary recommended treatment methods for LCNEC are the same as those recommended for NSCLC. Patients with early-stage LCNEC are primarily treated with surgery, and those at middle and advanced stages require multidisciplinary treatment. Most patients with early-stage LCNEC are treated with surgery ⁷; however, surgery alone is insufficient to treat LCNEC. Iyoda et al. retrospectively analyzed 335 cases of pathologic stage IA NSCLC and found that large-cell neuroendocrine histology is a significant adverse prognostic factor ⁸. Therefore, surgical resection alone represents an insufficient treatment for LCNEC. Saji et al. retrospectively evaluated the efficacy of perioperative chemotherapy for patients with completely resected LCNEC and found that the patients who underwent surgery alone were 9.5 times more likely to die compared with patients who received surgery combined with chemotherapy. Therefore, perioperative chemotherapy is needed to improve survival in patients with LCNEC ⁹. The most common chemotherapy used was the platinum-based combinations of VP-16 and CPT-11 ⁹. Sun JM et al. evaluated whether an advanced LCNEC should be treated similarly to an SCLC or NSCLC. The treatment for advanced LCNEC, similar to SCLC, is more appropriate compared with that for NSCLC ^{10 11}.

LCNEC is a biologically heterogeneous group of tumors comprising distinct subsets based on genomic signatures: SCLC-like subset (TP53 + RB1 co-mutation/loss and other SCLC-type alterations), NSCLC-like subset (lack of co-altered TP53 + RB1 and a nearly universal occurrence of NSCLC-type mutations [STK11, KRAS, and KEAP1]), and carcinoid-like subset (MEN1 mutations and low mutation burden) ¹². The analysis of our patient's tumor by NGS revealed RB1 (c.1759G > T[p.E587*]) mutation, KEAP1 (c.1436A > T[p.D479V]) mutation, STK11 (c.616del[p.A206fs]) mutation, TP53 (c.230del[p.P77fs]) ERBB2 (c.3283G > A[p.A1095T]) mutation, SMARCA4 (c.2921C > T[p.P974L]) mutation, and SMAD4 (c.473T > A[p.V158E]) mutation. As the molecular characteristics of the patient accompanied with NSCLC-type (STK11 and KEAP1) and SCLC-type mutations (TP53 and RB1), we treated him with the DP regimen, which was effective for both diseases.

PD-1 inhibitors, such as pembrolizumab or nivolumab, are ICIs that are proven to improve overall survival in advanced NSCLC ^{13 14}; however, data about the efficacy of ICIs in L-LCNEC are rare and limited mainly to some small sample clinical trials or a few case reports. Sherman et al. analyzed 37 patients with advanced LCNEC and found that patients treated with ICIs had a longer median OS because advanced disease diagnosis was longer in patients treated with ICIs than those who were not ¹⁵. In this context of limited data on the efficacy of ICIs in advanced LCNEC, little is known about their use in association with

chemotherapy. The NADIM study indicated that neoadjuvant chemoimmunotherapy could change the perception of locally advanced NSCLC as a potentially lethal disease to one that is curable ¹⁶. There is some data on the efficacy of neoadjuvant chemoimmunotherapy in patients with advanced LCNEC. Our patient with LCNEC received a complete tumor response after receiving sintilimab plus platinum-based chemotherapy. Sintilimab, a highly selective, fully human monoclonal antibody, blocks the interaction of PD-1 and its ligand, PD-L1. Compared with nivolumab or pembrolizumab, sintilimab has a different binding site and potentially greater affinity against PD-1 as per the preclinical data ¹⁷. The ORIENT-11 study indicated the addition of sintilimab to chemotherapy with pemetrexed and platinum resulted in longer PFS than with chemotherapy alone in patients with advanced or metastatic nonsquamous NSCLC ¹⁸. Likewise, in our case, the postoperative pathology of the patient suggested a complete response, recommending that sintilimab and chemotherapy have a synergistic anticancer effect.

4. Conclusion

LCNEC is a rare subset of lung cancer with a poor prognosis. The efficacy of ICIs in LCNEC has not yet been evaluated, but they might have certain advantages regarding survival. Immunotherapy combined with chemotherapy has been proven to prolong survival in patients with advanced NSCLC. In previous studies, neoadjuvant chemoimmunotherapy may turn some advanced NSCLC into curable diseases. However, further studies are still needed to confirm the role of neoadjuvant chemoimmunotherapy in advanced LCNEC.

Declarations

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Authors' contributions

XBY and WYW: conception and design and final approval of the manuscript. JPH and FYW: wrote the first draft of the manuscript. XHD, YFL, ZYG, YYZ and SQL: collected the data. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Abbreviations

LCNEC: large-cell neuroendocrine carcinoma; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; ICIs: immune checkpoint inhibitors; PET-CT: positron emission tomography combined with computed tomography; NGS: Next-generation sequencing.

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Figures

Figure 1

Evaluation by FDG PET-CT at diagnosis. The mass in the superior lobe of the right lung was considered as the primary tumor.

Figure 2

Pathology at the time of diagnosis. Left: hematoxylin and eosin (HE) staining shows neoplastic cells with morphological characteristics of NSCLC. Right: immunohistochemistry reveals a diffuse expression of cytokeratin, leading to the diagnosis of lung LCNEC. Picture magnification: 20x; scale bar: 50 μm.

Figure 3

CT scan showing an decreased tumor size in the right lung.

Figure 4

At the time of surgery. Left: HE staining shows a phagocytic reaction in the necrotic area of former cancer tissue, with no residual viable cancer cells. Right: HE staining displays a collagen fiber hyperplasia in the necrotic area of former cancer tissue, with no residual viable cancer cells. Picture magnification: 20×; scale bar: 50 μ m. Color online.