Successful treatment with temozolomide in an elderly woman with advanced pulmonary large-cell neuroendocrine carcinoma
A case report
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Abstract
Rationale: Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is a rare type of lung cancer, and 40% of patients are in stage IV at initial diagnosis. It has an extremely poor prognosis with a 1-year survival rate of 27%. Patients with LCNEC are predominantly male, older, and heavy smokers. There has been no clinical trial conducted to determine the best treatment for advanced LCNEC. Temozolomide (TMZ) has been successfully used to treat a variety of malignancies, such as glioblastoma multiforme, astrocytoma, non-small-cell lung carcinoma. However, its efficacy in advanced stage pulmonary LCNEC has rarely been studied.
Patient concerns: We present the rare case of a 69-year-old woman with advanced pulmonary LCNEC. She complained of recurrent dry cough for more than 1 month.
Diagnoses: After chest computed tomography (CT) and biopsies of supraclavicular lymph nodes, the diagnosis of stage IIIB LCNEC of the lung was made.
Interventions: Four cycles of chemotherapy with etoposide and cisplatin was administered as the first-line regimen. As the disease progressed, we administered icotinib and liposomal paclitaxel. Finally, we administrated TMZ as the third-line regimen.
Outcomes: The patient showed partial response after 5 months. She has survived for 19 months from the time of diagnosis with a good performance status.
Lessons: TMZ appears to be an efficacious option to treat elderly patients with advanced LCNEC.

Abbreviations: CT = computed tomography, EGFR = epidermal growth factor receptor, LCNEC = large-cell neuroendocrine carcinoma, NSCLC = non-small-cell lung carcinoma, PR = partial response, SCLC = small-cell lung cancer, TKI = tyrosine kinase inhibitor, TMZ = temozolomide, VP-16 = etoposide.

Keywords: advanced pulmonary large-cell neuroendocrine carcinoma, elderly woman, temozolomide

1. Introduction
Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is a high-grade neuroendocrine tumor. Although LCNEC has been categorized as a variant of large-cell carcinoma, the biological behaviors of LCNEC resemble those of small-cell lung cancer (SCLC). The clinical manifestations include cough, expectoration, hemoptysis, and chest pain. It often occurs in older men with heavy smoking histories. Forty percent of patients are in stage IV at initial diagnosis due to the disease’s insidious onset.[1] Patients with LCNEC have a poor prognosis with a 5-year survival rate of 13 to 57%.[2] Four to six cycles of etoposide combined with cisplatin or carboplatin chemotherapy is generally recommended for advanced LCNEC.[3] There have been few reported cases of pulmonary large-cell neuroendocrine tumor accompanied by abdominal lymph node metastasis. The treatment of temozolomide (TMZ) in advanced stage pulmonary LCNEC has rarely been reported. We present the rare case of a 69-year-old woman with stage IIIIB pulmonary LCNEC who showed a good response to TMZ. The patient has achieved long-term survival of 19 months due to multidisciplinary treatment.

2. Case report
A 69-year-old woman was admitted to the hospital in December 2016. She complained of a recurrent dry cough for more than 1 month. The patient had a history of hypertension and diabetes and no history of smoking. Physical examination did not indicate any abnormalities. A chest computed-tomography (CT) scan revealed a 34 × 30 mm lesion located in the right pulmonary hilum, with an enlargement of the right supraclavicular and mediastinal lymph nodes. Pathological examination of the right supraclavicular lymph node indicated metastatic cancer invasion.
The patient’s tumor was negative for thyroid transcription factor 1, Napsin, protein 40, and cell keratin 5/6 but positive for cluster of differentiation 56, cell keratin 7, synaptophysin, and chromogranin A, which supported the histological diagnosis of clinical stage IIIB LCNEC with a pulmonary origin. The diagnosis of LCNEC was confirmed by the pathology expert of the Shanghai Traditional Chinese Medicine Integrated Hospital. No other metastases were detected using an abdominal CT scan.

Four cycles of chemotherapy with etoposide (VP-16) and cisplatin were administered as the first-line regimen. Grade III bone marrow suppression appeared after chemotherapy, and our patient’s general condition deteriorated to the Eastern Cooperative Oncology Group performance status of 2. Therefore, she was unable to tolerate continuation of this chemotherapy regimen. A genetic test was performed on August 7, 2017. The epidermal growth factor receptor (EGFR) mutation status of the tumor was an EGFR 19 locus mutation. Subsequently, the patient was treated with icotinib, an EGFR tyrosine kinase inhibitor (TKI). Three weeks later, the patient developed bloating and decreased defecation. An abdominal X-ray revealed intestinal obstruction, and an abdominal CT scan indicated multiple retroperitoneal lymph node enlargements. Furthermore, positron emission tomography-CT demonstrated hypermetabolism of lymph nodes in the abdominal cavity, which was considered an indication of progressive disease. Therefore, we discontinued the treatment with icotinib, and two cycles of chemotherapy with liposomal paclitaxel were administered as the second-line regimen, with stable disease as the anticipated maximum response. In December 2017, our patient still felt bloated, and her lung tumor had grown to 41 × 19 mm (Fig. 1). Five cycles of chemotherapy with TMZ was then administered as the third-line regimen. She received TMZ orally once a day at a dose calculated according to her body surface area (150 mg/m²); she received 200 mg/day on days 1 through 5 of a 28-day cycle. Her symptoms, of bloating and decreased defecation completely disappeared. Her lung tumor decreased to 20 × 10 mm in size (Fig. 2); the tumor response was evaluated and considered a partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (1.1). As of this writing, the patient has survived for 19 months from the time of diagnosis with a good performance status (Karnofsky 80%).

3. Ethics approval and consent to participate

This study was approved by the Ethics Committee of Dongyang People’s Hospital. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

4. Discussion

Pulmonary LCNEC is a rare type of lung cancer that accounts for 0.9% of all primary lung malignancies, and 40% of patients are in stage IV at initial diagnosis.[13] Since the biological behavior of LCNEC has been reported to be similar to that of SCLC, patients with LCNEC are often misdiagnosed and have an extremely poor prognosis comparable to that of SCLCs.[4,5] with a 1-year survival rate of 27%[6] and a 5-year survival rate of 13 to 57%.[2] Various series reports have indicated that 85 to 98% of patients who had a surgical resection for LCNEC had a history of cigarette smoking. The mean age of patients treated for LCNEC ranged from 62 to 68 years with a median of 65.8 years.[7–11] Patients with LCNEC are predominantly male, older, and heavy smokers.[4,8,12] The median overall survival of stage IV LCNEC patients was 4.0 months, in a population-based cancer registry of the Netherlands. The survival rate of LCNEC is inferior to that of other non-small-cell lung cancer (NSCLC) tumor types.[11]

LCNEC is most often responsive to platinum-based induction chemotherapy, with response rates of 60 to 80%.[13–15] Non-platinum chemotherapy is less effective, with response rates of 11%.[13] As LCNEC is very rare, there have been no clinical trials conducted to determine the best treatment for advanced LCNEC; recommendations for its treatment are based on extrapolation of the treatment methods used for NSCLC and SCLC patients, as well as published reports. Considering LCNEC’s supposed biological relation to SCLC and the comparable response rate, four to six cycles of etoposide combined with cisplatin or carboplatin chemotherapy is generally recommended for advanced cases.[13] EGFR mutations have been found to be very minor components of both SCLCs and LCNECs; however, they may be seen more frequently in combined histology.[16–18] Niederst et al[19] reported that treatment with EGFR-TKIs might be effective.

TMZ is an orally administered alkylating drug that is well tolerated by glioma patients as well as elderly outpatients. Moreover, TMZ has been successfully used to treat a variety of malignancies, such as glioblastoma multiforme, astrocytoma, NSCLC, melanoma, and breast cancer.[20,21] The current National Comprehensive Cancer Network treatment guidelines recommend TMZ for the treatment of neuroendocrine carcinomas. However, the efficacy of TMZ in stage IV pulmonary LCNEC has rarely been studied.
In this case, an elderly woman was in stage IV pulmonary LCNEC at initial diagnosis; thus, she had lost her opportunity for surgery. Four cycles of chemotherapy with VP-16 and cisplatin were administered as the first-line regimen. As the disease progressed, we administered icotinib and liposomal paclitaxel. Finally, we administered TMZ, an effective treatment for neuroendocrine neoplasms. She achieved PR after five cycles of chemotherapy with TMZ. She has a good performance status approximately 19 months after the initiation of treatment.

In conclusion, we suggest that a TMZ regimen can be an appropriate option for elderly patients with advanced LCNEC, even after multimodal therapy.

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