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Review Article

Biological and Clinicopathological Features of Pulmonary Large-cell Neuroendocrine Carcinoma-A New Era of Research

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ABSTRACT: Large-cell neuroendocrine carcinoma (LCNEC) of the lung, categorized as a lung neuroendocrine tumor, shows clinicopathological features similar to those of small-cell lung carcinoma (SCLC), although there are some differences between them. As patients with LCNEC have a very poor prognosis, and surgery alone does not provide a cure for it, a new treatment strategy including adjuvant chemotherapy after surgery is needed. Several studies have compared the biological behaviors of LCNEC and SCLC, which, in addition to their clinicopathological features, are very similar. Recently, the biological features of LCNEC related to molecular targeted therapies have been investigated, and new treatment strategies, such as mTOR (mammalian target of rapamycin) inhibitors, have been proposed for patients with LCNEC. Here, I discuss the current biological and clinicopathological features of LCNEC and introduce recent new research on it. LCNEC was reclassified from a variant of large-cell carcinoma to a neuroendocrine tumor. Consequently, the focus of studies on LCNEC switched from clinicopathological features to molecular targeted therapies, and research on LCNEC entered a new era. Further studies are needed to improve the prognoses of patients with LCNEC.

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KEYWORDS: large-cell neuroendocrine carcinoma, lung, surgery, adjuvant chemotherapy, profiling

Introduction

Large-cell neuroendocrine carcinoma (LCNEC) was proposed as a new category of tumors by Travis et al. in 1991.[1] The World Health Organization (WHO) originally classified LCNEC as a variant of large-cell carcinoma in 1999.[3] However, in 2015, LCNEC was reclassified as a neuroendocrine tumor, together with typical carcinoids, atypical carcinoids, and small-cell lung carcinoma (SCLC),[4] because its clinical and biological characteristics are different from those of classic large-cell carcinoma and similar to those of SCLC, which is a high-grade neuroendocrine tumor.[1] These changes may imply that studies on LCNEC need further work, and therefore no consensus has been reached on the treatment strategy for patients with LCNEC.[5] In this review article, I focus on the relationship between the biological and clinicopathological features of LCNEC and the current treatment

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strategies, and introduce new research on LCNEC.

Several questions on the treatment strategy for patients with LCNEC are as follows:

- Is SCLC-or non-SCLC-based chemotherapy better as an adjuvant chemotherapy for patients with LCNEC?
- Should adjuvant chemotherapy be given to patients with stage IA LCNEC?
- What are the surgical indications for patients with LCNEC, the clinical behaviors of which are very similar to those of SCLC?
- Can we perform limited resection in patients with sufficient lung function and general conditions for curative resection?

In this review, I discuss these clinical questions.

Clinical Features of LCNEC

Despite numerous recent reports on the clinicopathological features of LCNEC, most are retrospective studies of surgical cases, because most patients with LCNEC are diagnosed based on surgical specimens,[1, 5] as it is very difficult to diagnose LCNEC preoperatively. Therefore, the clinicopathological features of unresectable cases of LCNEC are still unclear. The clinical characteristics of patients with LCNEC of the lung are similar to those of patients with SCLC of the lung in many aspects, such as sex, age, smoking status, response to chemotherapy, and prognosis.[5] However, there may be some differences between LCNEC and SCLC,[1] and some reports revealed that the features of LCNEC are more similar to those of large-cell carcinoma than to SCLC.[6–8]

Many patients with LCNEC of the lung who undergo surgical resection are reported to experience recurrence as distant metastases[5] and to have poor prognoses, with 5-year survival rates of 15-57%.[9–19] Moreover, even patients with pathological stage I LCNEC have poor prognoses, with 5-year survival rates of 27-67%,[13–18] compared with patients with non-SCLC.[10, 20] Because surgery alone is not sufficient to treat patients with LCNEC[21–32], some retrospective and prospective studies on adjuvant chemotherapy have been performed (Table 1). These studies suggested that adjuvant chemotherapy may be effective in patients with LCNEC, although one study showed no effect.[33] Interestingly, only one report revealed that octreotide, which is used to treat carcinoid tumors, was effective as an adjuvant therapy for LCNEC.[34]

Which is Better as Adjuvant Chemotherapy for Patients with LCNEC: SCLC-or non-SCLC-based chemotherapy?

Most studies on chemotherapy responses revealed that SCLC-based chemotherapy is effective in patients with advanced or unresectable LCNEC, including recurrence after complete resection or suspicious cases diagnosed by biopsy, comparable with patients with SCLC[35–40]; yet some reports revealed an inferior response in patients with LCNEC compared with SCLC.[41, 42] The American Society of Clinical Oncology guidelines revealed that patients with stage IV LCNEC might receive the same treatment as those with non-small-cell carcinoma or a combination of etoposide and platinum.[43] In addition, the Update Committee proposed that the etoposide plus platinum combination provides optimal efficacy in treating LCNEC.[43] Nedaplatin plus irinotecan[44] or amrubicin monotherapy[45] may also be optimal chemotherapy regimens for LCNEC. Treatments for LCNEC in other organs may also be based on those for LCNEC in the lung.[46–52]

Should We Perform Adjuvant Chemotherapy for Patients with Stage IA LCNEC?

Even stage I LCNEC is associated with a poor prognosis.[1] Such patients may have a significantly worse prognosis than those with stage IA adenocarcinoma/squamous cell carcinoma.[20] Patients with LCNEC have a high recurrence rate, with recurrence involving mainly distant metastases.[14] Although there are no studies on adjuvant chemotherapy for stage IA LCNEC, studies demonstrate that adjuvant chemotherapy is effective for stage I LCNEC.[21, 30]

Surgical Indications for Patients with LCNEC

As mentioned above, LCNEC is diagnosed after surgical resection because of the difficulty in diagnosing it preoperatively.[1, 4] However, some cases are diagnosed with LCNEC or suspected LCNEC preoperatively.[36–38, 53] If such patients have clinical stage II or III, can we recommend chemoradiotherapy? Some reports revealed non-inferior response rates to chemotherapy in patients with LCNEC, comparable with those in patients with SCLC.[36, 37] Those reports did not show a complete response for LCNEC even when chemoradiotherapy was used, although some patients with SCLC achieved a complete response to chemotherapy.[36, 38] These results suggest that a complete

response of LCNEC to chemotherapy might not be possible, but only a partial response, even though chemotherapy yields high response rates and appears to be as effective as an adjuvant treatment after tumor resection in LCNEC.[5, 36, 38] For SCLC, curative surgical resection should be performed only for clinical stage I, because stage II or higher stages show high recurrence rates and poor prognoses after surgery; rather, chemoradiotherapy is the optimal treatment and can even yield a complete response. On the other hand, surgical resection is ideal for resectable stage II or III LCNEC according to retrospective studies showing that curative surgical resection with adjuvant chemotherapy was effective for LCNEC, even in an advanced stage, and because a complete response to chemoradiotherapy cannot be expected.[5, 54]

Can We Perform Limited Resection in Patients with Sufficient Lung Function and General Conditions for Curative Resection?

Recently, limited resection has been performed in patients with small-sized adenocarcinoma showing mainly ground glass opacity,[55] but very rarely in patients with LCNEC. Previously, we revealed that patients with LCNEC, even stage I, had poor prognoses.[1] Only one retrospective study has been performed on limited resection for LCNEC, in which four of five patients who underwent the resection had poor prognoses, and only one survived without recurrence.[23] If possible, standard curative resection should be performed for LCNEC, even that of small size.[23]

Cytological and Pathological Features of LCNEC

It is very difficult to diagnose LCNEC preoperatively because of the small size of biopsy specimens.[4] The criteria for LCNEC diagnosis include neuroendocrine morphology, mitotic rate > 10 per 2 mm^2, and neuroendocrine differentiation confirmed by immunohistochemical staining for neuroendocrine markers such as chromogranin, synaptophysin, and neural cell adhesion molecule.[4] Differential diagnoses for LCNEC include SCLC, atypical carcinoids, poorly differentiated adenocarcinoma, basaloid squamous cell carcinoma, large-cell carcinoma with neuroendocrine morphology,[10, 56, 57] and large-cell carcinoma with neuroendocrine differentiation.[10] LCNEC shows cytomorphological characteristics different from those of classic large-cell carcinomas,[58] including significantly higher expression rates of Bcl-2 and Ki-67.[59] The expression of 34betaE12 and thyroid transcription factor-1 may be useful in distinguishing LCNEC from basaloid carcinoma.[60] The differences between LCNEC and SCLC include cell size and immunohistochemical positivity for neuroendocrine markers. The differences between LCNEC and atypical carcinoids are mitosis and positivity of immunohistochemical staining for neuroendocrine markers. Although SCLC and atypical carcinoids highly express immunohistochemical neuroendocrine markers, their expression is not necessary for a diagnosis of SCLC or atypical carcinoids. It is difficult to evaluate the characteristic morphological features, neuroendocrine features, or mitotic count in small biopsy specimens. LCNEC specimens do not necessarily exhibit diffuse positivity for immunohistochemical neuroendocrine markers and sometimes show patchy positivity. When diagnosing tumors as LCNEC, such features should be taken into consideration.[61]

Biological Features of LCNEC

Before its proposal in 1991 by Travis et al. as a fourth category of neuroendocrine tumors of the lung, LCNEC was described by other authors,[62, 63] and its biological features have been investigated since 1991. Neuroendocrine tumors of the lung were categorized as typical carcinoids, atypical carcinoids, and SCLC before 1999,[64] and there have been many studies on the biological features of LCNEC using comparative genomic hybridization (CGH), genetic profiling, microsatellite markers, or immunohistochemical staining for biological markers since the its classification by the WHO in 1999.[1, 3, 5] In 1999, analyses using microsatellite markers revealed that loss of heterozygosity was more frequent among high-grade neuroendocrine tumors, including LCNEC and SCLC, than among typical and atypical carcinoids.[65] LCNEC exhibited different expression levels of Ki-67/p53/Rb[66] and Bcl-2[67] and higher proliferation compared with carcinoids.[68] LCNEC was similar to SCLC in terms of p53, Kras 2, and C-raf-1 expression,[69] with high telomerase activity.[70] LCNEC and SCLC differed from typical and atypical carcinoids in the expression of p53 and Rb.[71] CGH and array-based CGH analyses revealed both common and differential expression between LCNEC and SCLC.[72, 73] Immunohistochemical staining analyses also revealed common and differential expression between LCNEC and SCLC,[74] as

Table 1 Literature on adjuvant chemotherapy for patients with large-cell neuroendocrine carcinoma

Author	Design	Effect	Year	Journal
Dresler CM	retrospective	negative	1997	Ann Thorac Surg
Iyoda A	retrospective	positive	2001	Cancer
Rossi G	retrospective	positive	2005	J Clin Oncol
Iyoda A	prospective	positive	2006	Ann Thorac Surg
Veronesi G	retrospective	positive	2006	Lung Cancer
Saji H	retrospective	positive	2010	Anti-Cancer Drugs
Sarkaria IS	retrospective	positive	2011	Ann Thorac Surg
Kim KW	retrospective	positive	2017	World J Surg
Filosso PL	retrospective	positive	2017	Eur J Cardiothorac Surg

well as differential expression between LCNEC and classic large-cell carcinoma.[75] The gene expression profiles of LCNEC, SCLC, adenocarcinoma, and normal lung tissue obtained by microarray analysis were unable to distinguish LCNEC from SCLC.[76] LCNEC and SCLC were found to be similar in terms of clinicopathological features, but different in terms of certain biological behaviors.[72–75] Among LCNEC, SCLC, and classic large-cell carcinoma, analyses of microsatellite markers on chromosome 3p and of p16 methylation revealed similar patterns between LCNEC and SCLC, and p16 methylation patterns were similar between LCNEC and classic large-cell carcinoma.[77] LCNEC exhibited frequent loss of heterozygosity on chromosome 5q, and the presence of tumor suppressor genes on chromosome 5q in LCNEC was suggested.[78]

A New Era of LCNEC Research

Many reports have demonstrated that platinum-and SCLC-based chemotherapies are effective treatments for LCNEC, a high-grade neuroendocrine tumor.[79, 80] However, these treatments have not been sufficient to improve the prognoses of patients with LCNEC, especially those with an advanced stage. Therefore, novel treatments, including molecular targeted therapies, for LCNEC are needed.

Mutations in EGFR within exons 18,[81] 19,[82, 83] and 21[84, 85] have been reported in LCNEC, albeit infrequently.[81, 84, 86]

Because neuroendocrine tumors of the lung are characterized by overactivation of the mTOR (mammalian target of rapamycin) pathway, mTOR inhibitors may be effective in treating LCNEC.[87] Analyses of genetic alterations in the PI3K/AKT/mTOR pathway were performed and showed similar profiles between LCNEC and SCLC.[88]

Inhibitors of the PD-1/PD-L1 immune checkpoint are effective treatments for lung carcinoma, and a relationship between PD-L1 expression and the effects of immune checkpoint inhibitors has been observed.[89] A PD-L1 expression rate of 10.4% was observed in LCNEC,[89] and the effectiveness of immune checkpoint inhibitors on LCNEC was demonstrated, even in the absence of PD-L1 expression.[90] Tropomyosin-related kinase B and brain-derived neurotrophic factor may also be therapeutic targets for LCNEC.[91] Anti-VEGF-, anti-c-KIT-, and anti-HER2-targeted agents may have potential roles in the treatment of LCNEC,[81] although anti-c-KIT-targeted therapy is controversial.[92–94] One case report revealed the successful treatment of metastasis to the iris from LCNEC by intravitreal anti-VEGF injection.[95]

Another report revealed that molecular subtypes based on RB1 expression might predict the outcome of chemotherapy in patients with LCNEC,[96] and three genomic subsets of LCNEC were proposed: small-cell carcinoma-like, non-small-cell carcinoma (predominantly adenocarcinoma)-like, and carcinoid-like.[97, 98] On subtypes of LCNEC, these results may be able to explain that clinicopathological and biological behaviors of patients with LCNEC have features of both SCLC and non-SCLC, although many features of LCNEC are very similar to those of SCLC. Further studies to evaluate these results are warranted.

Conclusions

LCNEC was reclassified from a variant of large-cell carcinoma to a neuroendocrine tumor, and subsequent studies shifted their focus from their clinicopathological features to molecular targeted therapies. As a result, research on LCNEC was said to have entered a new era at the time. We need to continue this research to improve the poor prognoses of patients with LCNEC.

Conflicts of interest: Non declared.

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April	2001 to	Staff Surgeon, Department of Thoracic Surgery,
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April	2008 to	Assistant Professor, Department of Thoracic Sur-
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October	2008	Associate Professor, Department of Thoracic Surgery, Kitasato University, School of Medicine, Kanagawa
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2003	Young Investigator Award, The 20th Annual meeting of the Japanese Association for Chest Surgery
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