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Pulmonary Large-Cell Neuroendocrine Carcinoma
From Epidemiology to Therapy

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Abstract: Lung neuroendocrine tumors are a heterogeneous subtype of pulmonary cancers representing approximately 20% of all lung cancers, including small-cell lung cancer (SCLC) and large-cell neuroendocrine carcinoma (LCNEC). The frequency appears to be approximately 3% for LCNEC. Diagnosis of LCNEC requires attention to neuroendocrine features by light microscopy and confirmation by immunohistochemical staining for neuroendocrine markers. Both SCLC and pulmonary LCNEC are high-grade and poor-prognosis tumors, with higher incidence in males and smokers and peripheral localization. LCNEC is very rare, and the precise diagnosis on small specimens is very difficult, so we have still too few data to define a standard of treatment for pulmonary LCNECs. Data of literature, most based on retrospective analysis, indicated a poor 5-year overall survival, with a high incidence of recurrence after surgery, even in stage I disease. Primary surgery should be the first option in all operable patients because there is no validate therapeutic approach for LCNEC due to lack of clinical trials in this setting. Neoadjuvant platinum-based regimens remain only an option for potentially resectable tumors. In advanced stages, SCLC-like chemotherapy seems the best option of treatment, with a good response rate but a poor overall survival (from 8 to 16 months in different case series). New agents are under clinical investigation to improve LCNEC patients' outcome. We reviewed all data on treatment options feasible for pulmonary LCNEC, both for localized and extensive disease.

Key Words: Lung neuroendocrine tumors, Large-cell neuroendocrine carcinoma, Pathologic characterization, Cancer treatment.

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Lung neuroendocrine tumors are a heterogeneous group of cancers originating from neuroendocrine cells in the pulmonary and bronchial epithelium and represent 20% of all lung cancers.[1]

In the 1970s, pulmonary neuroendocrine tumors were classified into three histologically defined categories: typical carcinoids (TC), atypical carcinoids (AC), usually defined as carcinoids, and the more undifferentiated entity represented by small-cell lung cancer (SCLC).[2] In 1991, Travis et al. introduced a new distinct category of lung cancer, defined as large-cell neuroendocrine carcinoma (LCNEC), which showed large cells with abundant cytoplasm, necrotic areas, a high mitotic rate, and neuroendocrine features. It shared some characteristics with SCLC, while differing because this latter presents smaller cells, with low nuclear/cytoplasm ratio and a different pattern of tissue invasiveness.[3] Later in 1999 and 2004, the World Health Organization recognizes LCNEC as a variant of large cell carcinoma (LCC), a type of non–small-cell lung cancer (NSCLC) and one of the four major types of lung neuroendocrine tumors.[4–6]

Currently, LCNECs are considered as a separate entity for clinical characteristics, histology, prognosis, and survival.

INCIDENCE AND EPIDEMIOLOGY

Pulmonary LCNECs are rare tumors of the lung: in a series of surgically resected cases, the incidence of pulmonary LCNECs appeared to be between 2.1% and 3.5%. However, the frequency appears to be higher than estimated because of difficulties in diagnosis on cytological specimens.[7]

Unlike TCs and ACs, LCNECs are often associated with male sex, older age (median age is 65 years), and heavy smoking habit[8–11] (Table 1).

CLINICAL PRESENTATION

Several characteristics differentiate LCNECs from carcinoids (TCs and ATs), indicating a more aggressive behavior. Patients with LCNECs are poorly symptomatic; cough, hemoptysis, or postobstructive pneumonia are infrequent. Sometimes, patients present an asymptomatic nodule or chest pain, nonspecific flu-like symptoms, dyspnea, night sweats, and carcinoid syndrome. Paraneoplastic syndromes are quite uncommon. At the moment of diagnosis, among pulmonary neuroendocrine tumors, LCNEC present high rate of lymph node (60%–80%) and distant metastasis (40%), similar to SCLC[8] (Table 1).

DIAGNOSIS AND STAGING

Diagnosis of LCNEC could be suggested by conventional radiograph of the chest and computed tomography scan. There are no specific findings in conventional

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TABLE 1. Main Clinicopathologic Characteristics of Pulmonary LCNECs[a]

Sex	Primarily in male patients (M:F = 17:1)
Median age (yr)	Older (median age, 65 yr)
Smoking status	Heavy smokers
Incidence	2.1%–3.5% (in surgically resected cases)
Five-year and median survival	
Resectable stage I, %	33
Stage II, %	23
Stage III, %	8
Stage IV (median survival months)	9.2–12.6
Symptoms	
Infrequent	Cough
	Hemoptysis
	Postobstructive pneumonia
Sporadic	Asymptomatic nodule
	Chest pain
	Dyspnea
	Night sweats
	Carcinoid syndrome
Uncommon	Paraneoplastic syndromes
Lung location	Peripheral or midzone
Differentiation grade	High
Neuroendocrine markers	Chromogranin A
	Neuron-specific enolase
	Synaptophysin
	Somatostatin
Mitotic count per 2 mm^2 field	>11 mitoses/10 high power field
Necrosis	Extensive
Cell histology	Large cells
	Low nuclear/cytoplasm ratio
	Significant nuclear pleomorphism
	Atypical nucleoli
Growth pattern	Organoid growth pattern
	Extensive areas of necrosis
	Cellular palisading pattern or rosette-like areas
Lymphatic metastases at diagnosis	60%–80%
Distant metastases at diagnosis	40%
Treatment	Surgery and neoadjuvant or adjuvant chemotherapy and/or RT for early stages (I to II)
	Multimodal treatment (stage III)[1]
	Chemotherapy for advanced stage (IV)[b]

[a]Multimodal treatment includes computed tomography and/or RT.
[b]Chemotherapy includes etoposide- and platinum-based regimens.
LCNECs, large-cell neuroendocrine carcinomas; RT, radiotherapy.

radiographic examination; LCNECs often are peripherally located expansively growing lesions with irregular margins, with unspecific calcifications in 10%.[12] Bronchoscopy and staging are recommended. International Association for the Study of Lung Cancer suggested application of tumor, node, metastasis (TNM) staging to predict prognosis for neuroendocrine tumors.[13]

Because neuroendocrine tumors frequently express somatostatin receptors (SSTR), mostly type 2 (68%),[14] SSTR scintigraphy diagnostic techniques have been used for their imaging work-up. In particular, OctreoScan (indium 11-tagged diethylenetriaminepentaacetic acid pentreotide scintigraphy) targets with high-affinity SSTR2, SSTR3, and SSTR5, whereas 111In-DOTA-TOC (111In-DOTA-DPhe1-Tyr3-octreotide) and 111In-DOTA-LAN (111In-DOTA-lanreotide) targets, especially, with SSTR2 and SSTR5. These imaging procedures have been proposed to be used in preoperative staging and in postoperative follow-up of LCNEC, but there is still no evidence supporting their use in clinical practice, as it is for F-18 fluorodeoxyglucose positron emission tomography imaging, which is still controversial. Indeed, in neuroendocrine tumors, F-18 fluorodeoxyglucose positron emission tomography can have a minor sensitivity than 111In-DOTA-TOC and 111In-DOTA-LAN in detecting metastatic lesions, expecially for those located in mediastinum.[15]

Pulmonary LCNECs diagnosis often requires immunohistochemical staining and sometimes electronic microscopy to identify clear marks of neuroendocrine differentiation, which are difficult to perform on small biopsies or cytology specimens. Consequently, diagnosis is rarely enunciated without surgery.[5]

PATHOLOGIC CHARACTERIZATION

Histologic features of pulmonary LCNEC include large cell size (similar to three or more lymphocytes), areas of abundant necrosis, low nuclear/cytoplasm ratio, neuroendocrine differentiation growth pattern such organoid nests, trabecular, rosette and palisading features, a variably granular pattern of chromatin, clear or atypical nucleoli, and high mitotic rate (11 or more mitoses per 10 high-power fields)[16–19] (Table 1).

Foci of squamous or adenomatous differentiation sometimes coexist in these tumors, creating mixed pathologic entities called "*mixed LCNEC*." Although prospective data seem to be uncertain, mixed LCNEC exhibit an aggressive behavior, with a 5-year overall survival (OS) of 30%, quite similar to "*pure LCNEC*."[20]

LCNEC and AC share some pathologic features, such as growth patterns and necrosis, so differential diagnosis may be challenging. For instance, AC presents fewer mitotic figures and LCNEC exhibit much more necrosis.[18] Indeed, a mitotic rate of 11 mitoses or more per 10 high-power fields is a key factor to differentiate LCNEC and SCLC from AC.[21] Moreover, with respect to basaloid carcinoma, it presents more often comedo-like necrosis compared with the abundant one of LCNEC, and in addition, it does not express generally neuroendocrine markers.[18]

To achieve a more precise diagnosis, a careful pathologic review is recommended because it is quite easy to mistake an LCNEC for a poorly differentiated NSCLC, an AC and even an SCLC. The diagnosis of LCNEC is difficult on small biopsy or cytological samples and often described as non–small-cell lung carcinomas-not otherwise specified: these two terms referred to two different entities, not interchangeable expecially for treatment.[22]

IMMUNOHISTOCHEMISTRY

Pathologic diagnosis of NSCLC routinely uses a panel of immunohistochemical markers: cytokeratin (CK) 5/6, protein (p) 63, and p40 are squamous markers and thyroid transcription factor-1, napsin A, and CK7 are adenocarcinoma markers, whereas chromogranin A, synaptophysin, and CD56 are usually considered neuroendocrine markers. All the previous often are common to several lines of differentiation and may significantly overlap. Nevertheless, by using this panel of markers, an unspecific diagnosis of LCC could be better specified. Thus, approximately 60% to 70% of LCC can be reclassified as poorly differentiated adenocarcinoma, 10% to 20% as squamous carcinoma, and 5% only as LCNEC.[19]

Regarding immunohistochemistry analysis, pulmonary LCNECs express typical neuroendocrine markers such as chromogranin, neuron-specific enolase, synaptophysin, and somatostatin, which are necessary to obtain the diagnosis, whereas they are negative for high-molecular-weight CKs, typically expressed by SCLC and other neuroendocrine tumors[7] (Table 1).

Indeed, recent data show that LCNECs express higher levels of tropomyosin-related kinase B and brain-derived neurotrophic factor by immunohistochemistry than both non-neuroendocrine tumor and SCLC[23] although none of them is clearly enough to help in the differential diagnosis between LCNEC and the other pulmonary neuroendocrine tumors.

MOLECULAR MARKERS

Pulmonary LCNEC proliferative rate is higher than classic LCC and other low-grade neuroendocrine tumors, such as carcinoids. As SCLC, they show higher expression of Ki-67, Bcl-2, and p21 and of telomerase activity, abnormal p53, and absent Rb.[24] In particular, Onuki et al.[25] analyzed loss of heterozygosity (LOH) at 10 chromosomal regions and p53 mutations in 59 neuroendocrine tumors, including 18 LCNEC. They found high frequencies of LOH and p53 alterations in LCNEC (83% and 72%, respectively): p53 alternations were in 23% LOH, 31% point mutations, and 46% both. Abnormalities of p53 seemed to be correlated to poor survival. These data derive from single, small-size retrospective studies, so it is impossible to obtain realistic recommendations for clinical practice.

The bigger genomic-based classification of lung cancer produced by the Clinical Lung Cancer Genome Project and Network Genomic Medicine identified important similarities between LCNEC and SCLC, regarding also the transcriptome, amplified and deleted regions and mutated genes. Therefore, the authors suggest that to combine immunohistochemical and genomic analysis to differentiate each other.[26]

DIFFERENTIAL DIAGNOSIS BETWEEN SCLC AND PULMONARY LCNEC

SCLC and pulmonary LCNEC share several characteristics such as high incidence in males and smokers, high mitotic rate, variable neuroendocrine marker expression, high grade, poor prognosis, and some genetic alterations (i.e., *MEN1*gene mutation). Indeed, these two histotypes are often combined in the single entity of high-grade neuroendocrine carcinoma (HGNEC).[21]

LCNEC can be distinguished from SCLC using some morphologic criteria: larger cell size, abundant cytoplasm, polygonal shape (versus fusiform), less evident nuclear molding, and less DNA deposits in blood vessels[16] (Table 2).

Nitadori et al.[27] found a stronger CK7, CK18, E-cadherin, and beta-catenin expression in pulmonary LCNEC as compared with SCLC. However, despite the discrete body of evidence and studies, more prospective data are necessary.

PROGNOSIS AND SURVIVAL

Pulmonary LCNEC behaves biologically aggressive, similarly to SCLC. Stage by stage, survival curves of pulmonary LCNEC and SCLC overlap, and in addition, survival is lower than other NSCLCs. Prognosis is poor even in patients with potentially resectable stage I lung cancer with 5-year survival rates ranging from 27% to 67%.[28]

Regarding all stages, Iyoda et al.[28,29] revealed a 5-year survival rate of 35.3% and a 5-year disease-free survival rate of 27.4% (Table 1); great part of relapses occurred within the first 2-year follow-up. One of the causes of this dramatic issue is the development of second primary cancers, synchronous or metachronous.

TREATMENT

There is no standard treatment of pulmonary LCNEC, and only few data are available primarily from case series. Because it is a very rare disease, randomized clinical trials are difficult to be conducted. Five-year OS remains poor, despite multimodal treatment in advanced stages and incidence of recurrence after surgery is high even in stage I disease.[30]

Surgical Management

Primary surgery should be the first option in operable patients (TNM stages I and II). This approach constitutes also the principal way to obtain an accurate diagnosis. Unfortunately, the majority of pulmonary LCNEC are not eligible for surgical resection because of local or systemic spread. Instead, in early stages, lobectomy or pneumonectomy are the preferred choices because they may improve survival in the absence of lymph node metastases at mediastinal sampling[30] (Table 1).

Grand et al.[31] conducted a retrospective analysis to compare pulmonary LCNEC with LCC outcomes. They did not evidence any significant difference in terms of type of surgical approach (resection, lobectomy, or pneumonectomy) and OS. By contrast, they identified the rate of visceral pleura invasion as a frequent finding in combined LCNEC compared with pure LCNEC.

Mazières et al.[32] reported a case series of 18 patients with pulmonary LCNEC treated with radical surgery, followed by adjuvant radiotherapy in T3 and/or N2 cases. One-year survival rate was 27%, and there was no correlation with nodal status.

Zacharias et al.[30] suggested that an extended complete anatomical resection with a systematic nodal dissection may influence survival.

Definitely, surgery may be curative in approximately 30% of cases; therefore, optimization of perioperative treatments could improve outcome.

TABLE 2. Differential Diagnosis between SCLC and Pulmonary LCNEC

Feature	LCNEC	SCLC
Incidence	2.%1–3.5%	15%–20%
Clinical features	Male/smoker/older	Male/smoker/older
Lung location	Peripheral or midzone	Central
Mitotic rate	>11 mitoses/10 high power field	>11 mitoses/10 high power field
Cytology	Large cells	Small cells
	Abundant cytoplasm	Scarce cytoplasm
	Significant nuclear pleomorphism	Significant nuclear pleomorphism
	Prominent nucleoli	No prominent nucleoli
Growth pattern	Organoid, palisading	Diffuse sheets of cells
	Abundant necrosis	Abundant necrosis
IHC	Variable NE marker expression	Variable neuroendocrine marker expression
Lymphatic metastases at diagnosis	60%–80%	60%–80%
Distant metastases at diagnosis	40%	60%–70%
Five-year survival	15%–25%	<15%
Treatment	Surgery and neoadjuvant or adjuvant chemotherapy and/or RT for early stages (I to II)	Surgery and concurrent CT and RT (stages I to II)
	Chemotherapy and/or RT (stage III)	Concurrent CT and RT (stage III)
	Etoposide- and platinum-based regimens for stage IV	Etoposide- and platinum-based regimens for stage IV

CT, computed tomography; SCLC, small-cell lung cancer; LCNEC, large-cell neuroendocrine carcinoma; RT, radiotherapy; IHC, immunohistochemistry.

Adjuvant Setting

All potentially resectable pulmonary LCNEC (stage I–III) should be operated.[33] Perioperative, neoadjuvant,[33] or adjuvant chemotherapeutic treatment could be valid options to prevent disease relapse.[34]

Indeed, a retrospective analysis of 144 surgically removed pulmonary LCNEC revealed a better outcome although not statistically significant, with preoperative or postoperative chemotherapy in stage I disease, suggesting that adjuvant therapy has a promising role in earliest diagnosed disease.[35]

The optimum regimen has not been established yet; moreover, it is not clear whether pulmonary LCNEC should be treated such as an SCLC.

In 2006, Iyoda et al.[36] conducted a prospective single-arm study of cisplatin–etoposide chemotherapy, the standard regimen for SCLC, as adjuvant treatment in completely resected pulmonary LCNEC comparing outcomes with historical data of patients treated without platinum in the same institution. Five-year OS favored the study arm (88.9% versus 47.4 %) and 2-year disease-free survival was 86.7% versus 47.8%. Three years later, the same group confirmed the superiority of platinum-based adjuvant chemotherapy over a non-platinum adjuvant therapy or no adjuvant therapy. In addition, multivariate analysis showed that platinum-based adjuvant chemotherapy may have a significant impact on prognosis.[28]

More recently, a pilot adjuvant trial in HGNEC, including pulmonary LCNEC, enrolled patients to receive three to four cycles of cisplatin–irinotecan chemotherapy, after curative surgery. This study showed 3-year relapse-free survival of 74% and 3-year OS of 86%.[37]

On the basis of these studies, a phase III clinical trial of adjuvant cisplatin plus irinotecan versus etoposide has been designed and is still ongoing in Japan (Japan Clinical Oncology Group 1205/1206, UMIN000010298).[38]

Nevertheless, data presented are too much inadequate to provide a realistic recommendation because they all come from retrospective studies or studies having a too much little sample.

Currently, a defined biomarker of response to chemotherapy has been not yet identified. Skov et al.[39] studied the expression of ERCC1, a member of the nucleotide excision repair system, involved in the repair of platinum-induced DNA damage and its correlation with chemosensitivity in a small cohort of patients with neuroendocrine lung tumors (SCLC, TC, AC, and LCNEC). Although the authors found a different expression of ERCC1 among neuroendocrine tumors with higher levels in low-grade neuroendocrine tumors (79% of TC and 67% of AC) and lower levels in SCLC and LCNEC (19% of LCNEC and 10% of SCLC), this difference did not affected the median survival. Probably, the study population was too much little to gain significance.

Sarkaria et al.[40] examined the role of neoadjuvant platinum-based chemotherapy in LCNEC, without identifying a clear significance, but only a trend toward a better OS for patients treated with a multimodal treatment. Actually, it should not be used in such patients initially susceptible for surgery (Table 3).

The role of radiotherapy[32] in the treatment of local or advanced pulmonary LCNEC is still unclear, but some authors suggest its use in locally advanced disease setting. Prophylactic cranial irradiation, which is largely used in limited disease SCLC after partial or complete response (CR) to chemotherapy, is not currently recommended in pulmonary LCNEC patients.

TABLE 3. Adjuvant and Neoadjuvant Setting

Authors	Study	No. of Patients	Treatment	Survival	*p* Value
Iyoda et al.[36]	Phase II, one-arm nonrandomized	15	Cisplatin plus VP-16	88.9% at 5 yr	0.0252
Iyoda et al.[28]	Multivariate analysis	79	Platinum based	88.7% at 5 yr	<0.0001
Kenmotsu et al.[37]	Prospective phase II	23	Cisplatin plus irinotecan	86% at 3 yr	95% CI, 69%–95%
Sarkaria et al.[40]	Retrospective review of a prospective database	25	Platinum based (20 patients), Platinum/etoposide (15 patients)	51% at 5 yr	0.052

CI, confidence interval.

Metastatic Setting

There is not a consensus on standard treatment for recurrent or advanced LCNEC. Positive results with SCLC-based regimes in neoadjuvant and perioperative setting encouraged to use this strategy also in unresectable disease.[32,36,37]

In 2005, Rossi et al.[41] analyzed 83 cases of pulmonary LCNEC (65% metastatic patients), exploring clinical and therapeutic histories and performing immunohistochemical screening of several receptor tyrosine kinases to identify new potential therapeutic targets and better strategies of treatment. Review of clinical features confirmed prevalence of male sex, strong smoker habitus, median-age incidence, and peripheral location of lung lesion. Main sites of metastasization were brain, bone, and liver. Regarding chemotherapeutic strategies, their analysis confirmed in metastatic patients a greater efficacy of platinum–etoposide chemotherapy, with a response rate (RR) of 29%, including two cases of CRs and four partial responses (PRs); on the other hand, no CR or PR were observed in metastatic patients treated with different chemotherapeutic schemes. Immunohistochemical evaluation of receptor tyrosine kinases expression revealed positivity of platelet-derived growth factor receptor-β (81.9%), platelet-derived growth factor receptor-α (60.2%), met-protoncogene receptor tyrosyne kinase (47%), v-kit hardy-zuckerman 4 feline sarcoma viral oncogene homolog (62.7%), and stem cell factor (56.6%), which is c-KIT ligand always copresent with KIT. Interestingly, the only statistical significant correlation was found between MET positivity and OS, with a median OS of 18 and 24 months in MET positive and negative, respectively.[41]

In 2007, Fujiwara et al.[42] retrospectively analyzed outcomes from pulmonary LCNEC patients (22 patients, of which 20 were stage IIIB or IV or recurrent) receiving platinum plus irinotecan/taxanes/vinorelbine/etoposide or paclitaxel. PFS and objective response rate (ORR) on total patient population were 4.1 months and 59.1%, respectively. More efficacious regimes were platinum–paclitaxel (ORR, 71.4%) and platinum–irinotecan (ORR, 55.6%), with a median OS of 10.3 months and 1-year survival rate of 43%. All these results referred to a very small sample of patients: only four patients received platinum/etoposide, and survival of this subgroup was not reported.

Nevertheless, they are in agreement with those derived from the analysis of subgroups of LCNECs in previous studies.[43–45] The efficacy of these drugs needs to be confirmed by prospective multi-institutional trials.

It is becoming increasingly evident that LCNEC tends to share several characteristics with SCLC also in terms of chemotherapy response,[46,47] so efforts have been directed to clarify whether pulmonary LCNEC could be treated as SCLC, as NSCLC or as another variant of lung tumor.

Tokito et al.[48] analyzed differences in treatment response to various schemes of chemotherapy of so called pulmonary "possible LCNEC." The term "possible LCNEC" was introduced by Travis et al.[47] referring to NSCLC positive to neuroendocrine markers and with neuroendocrine morphologic features on small samples derived from biopsies. He reviewed 24 "possible LCNEC" and 10 "defined LCNEC," who underwent SCLC-like chemotherapy (platinum plus etoposide or irinotecan) in 67% and 60% of cases, respectively, finding no statistical differences in RR, PFS, or median survival time (median follow-up of 23.2 months). RR in "possible LCNEC" was 54%, similar to that obtained from previous analysis in the same setting: 50% by Igawa et al.[46] and 61% by Shimada et al.[49]

Thus, considering that the clinical efficacy of chemotherapy for unresectable LCNEC has been shown to be comparable with that for extensive disease SCLC,[46] new bigger and prospective trials for validation of SCLC-like approach both in defined and possible pulmonary LCNEC should be encouraged.

An interesting study on chemotherapy in pulmonary LCNEC patients has been published by Sun et al. 2 years ago.[50] They conducted a retrospective analysis on 45 pulmonary LCNEC patients treated with chemotherapy, stratifying them by SCLC therapy or standard NSCLC therapy and by sex, age, smoking habit, and neuroendocrine immunohistochemical pattern. The choice of chemotherapeutic strategy depended on oncologist decisions, so patients received different treatments: SCLC strategy was platinum–etoposide/irinotecan in 24.4% of patients and NSCLC strategy was platinum-based doublet (with gemcitabine, vinorelbine, pemetrexed, or taxanes) in 68.9%; only one patient received vinorelbine–gemcitabine and two patients received a TKI. OS was 16.5 months versus 9.2 months for SCLC-like treated patients versus NSCLC-like group, respectively. Median PFS was 6.1 versus 4.9 months, respectively. RR was 73% versus 50% for the two populations of treatment; interestingly, the best RR was obtained with platinum-based regimens (60% overall, 41% when combined with gemcitabine, 7% to pemetrexed) compared with nonplatinum based (11%) and TKI (0%). Probably due to the small number of patients, these results were not statistically significant but underlined the importance to use platinum in first-line therapy for pulmonary LCNEC.

Several reports investigated the activity of other therapeutic agents in advanced setting. Among whom, pemetrexed efficacy in pulmonary LCNEC was found to be very poor, and this evidence should be ascribed to the major levels of thymidylate synthase expressed by this histotype compared with other NSCLC subtypes.[51,52] Taxanes seemed to be more active, similarly to SCLC.[53] Instead, poor efficacy of TKI could be linked to the low percentage of EGFR-activating mutations in pulmonary LCNEC.[54]

In 2013, two multicenter phase II trials evaluated cisplatin-based combination chemotherapy in unresectable pulmonary LCNEC.[55,56]

In the first one, conducted by Le Treut et al.,[55] poor results on OS (8 months) were obtained with three to six cycles of cisplatin–etoposide chemotherapy in stage IIIB/IV LCNEC. It was a prospective, multicenter, single-arm, phase II study, with ORR as primary end point. Among 42 patients enrolled, only 29 diagnoses were centrally confirmed. In this subgroup stable disease occurred in 31% of patients, PR in 34% and progression disease in 35%; median PFS was 5 months and median OS was 8 months. All these results were not significantly different from total population and confirmed a worse prognosis.

In the second one, Niho et al.[56] demonstrated that cisplatin–irinotecan could be an efficacious first-line chemotherapy option in stage IIIB or IV pulmonary LCNEC. Forty-four patients were enrolled in this single-arm study with RR as primary end point. Forty-one samples were centrally revised and reclassified as LCNEC (30 patients), SCLC (10 patients), and NSCLC with neuroendocrine structure (one patient). RR was 46.7% for LCNEC reclassified patients versus 80% in the 10 cases reclassified as SCLC. Median survival was 12.6 and 17.3 months, respectively, suggesting not only a worse prognosis of LCNEC compared with SCLC but also a minor chemoresponsiveness. Despite some limitations of this trial including statistical biases, small sample size (only 10 SCLC patients), and lack of information on second-line treatments, this is the first study that have evaluated prospectively this chemotherapeutic scheme in pulmonary LCNEC patients (Table 4) although it was as not designed to compare RR, PFS, and OS across different histology groups.

TREATMENT AFTER FIRST LINE

Options for second-line treatment of SCLC are regimens including anthracyclines such as vinblastin, epirubicin/adriablastin, and cysplatinum.

The most investigated drug in this setting is amrubicin, a synthetic topoisomerase II inhibitor, extensively investigated in SCLC[57] and currently approved for SCLC in Japan and not by U.S. Food and Drug Administration or European Medicines Agency.

In a retrospective revision, 18 LCNEC patients pretreated with platinum-based chemotherapy were treated from 2002 to 2008 with amrubicin single agent in second (72%) or subsequent lines of therapy (28%), with promising results. ORR resulted of 27.7% (5 PR, with disease control rate disease control rate of 61%), PFS was 3.1 months, and OS of 5.1 months[58] (Table 3). Moreover, amrubicin treatment showed modest efficacy also in third/fourth lines of therapy.[59]

FUTURE DIRECTIONS

Few data are available on biological treatment in pulmonary LCNEC. Rossi et al.[41] in 2005 analyzed molecular profile of 83 LCNEC patients and the correlation with clinical outcome, identifying a significant correlation between MET

TABLE 4. Metastatic Setting

Authors	Study	Line	No. of Patients	Treatment	ORR (%)	mPFS (mo)	mOS (mo)
Fujiwara et al.[42]	Retrospective review	First	22	Cisplatin + irinotecan (n = 9), platinum + paclitaxel (n = 6), paclitaxel alone (n = 1), cisplatin + vinorelbine (n = 1), cisplatin + docetaxel (n = 1), platinum + etoposide (n = 4)	59.1%; 55.6% with irinotecan; 71.4% with paclitaxel (95% CI, 38.1–80.1)	4.1 (95% CI, 3.1–5.1)	10.3 (95% CI, 5.8–14.8). 10.3 with paclitaxel or irinotecan (95% CI, 0–21.8)
Sun et al.[50]	Retrospective review	First	45	SCLC regimen group: platinum + etoposide (n = 11); NSCLC regimen group: platinum + taxanes/gemcitabine/pemetrexed/vinorelbine or EGFR-TKIs (n = 34)	73% in SCLC group vs. 50% in NSCLC group (p = 0.19)	6.1 in SCLC group vs. 4.9 in NSCLC group (p = 0.41)	16.5 in SCLC group vs. 9.2 in NSCLC group (p = 0.10)
Le Treut et al.[55]	Prospective, multicenter, single-arm, phase II	First	29	Cisplatin + etoposide	—	5.0 (95% CI, 4.0–7.9)	8.0 (95% CI, 3.7–7.9)
Niho et al.[56]	Prospective, multicenter, phase II	First	30	Cisplatin + irinotecan	46.7% (95% CI, 28.3–65.7)	5.8 (95% CI, 3.8–7.8)	12.6 (95% CI, 9.3–16)
Yoshida et al.[58]	Retrospective review	Second and/or s.s.	18	Amrubicin	27.7 (95% CI, 9.7–53.5)	3.1 (95% CI, 0.9–5.7)	5.1 (95% CI, 2.2–9.7)

ORR, objective response rate; CI, confidence interval; SCLC, small-cell lung cancer; NSCLC, non–small-cell lung cancer; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; mPFS, median progression free survival; mOS, median overall survival; s.s., statistically significant.

positivity and OS: median OS was 18 and 24 months in MET-positive and MET-negative samples, respectively.

Recent reports describe the presence of EGFR-activating mutations, involving exons 19 or 21 in mixed LCNECs with an adenocarcinoma component, indicating that EGFR mutations should be evaluated in this specific setting.[60–63] Clinical responses to EGFR-targeted agent were, in fact, encouraging.

Angiogenesis is known to be one of the greater mechanism of tumor evolution; therefore, an important role could be played by inhibition of angiogenesis pathways, such as vascular endothelial growth factor, signal transducer and activator of transcription 1, and signal transducer and activator of transcription 3.[64] Recently, Mairinger et al.[65] explored how angiogenesis could be involved in LCNEC metastasization, hypothesizing the use of anti–angiogenetic-targeted drugs in association with chemotherapy.

Data of literature demonstrated a correlation between lymphangiogenesis and angiogenesis and hypoxia-inducible factor 1-α expression, a transcription factor that in response to hypoxia induces genes responsible of angiogenesis.[66,67] In particular, overexpression of fibroblast growth factor and Fms-reLated Tyrosine kinase 4 and the reduced expression of Kinase insert Domain Receptor and hypoxia-inducible factor 1-α seemed to predict a trend toward malignant behavior and worse outcome.[65]

New agents under clinical development include nedaplatin, a platinum-based antineoplastic drug, in combination with irinotecan[68] (Table 4).

Other innovative therapeutic targets could be represented by tropomyosin-related kinase B and brain-derived neurotrophic factor that are highly expressed in LCNEC as markers of invasiveness.[22]

To date, further studies are still needed to confirm positive data on all these drugs and especially better explore their use in pulmonary LCNEC to obtain the maximum effectiveness.

DISCUSSION

LCNEC of the lung is a rare tumor with a poor prognosis; because of biological and molecular features, they should be ascribed to the category of grade III neuroendocrine LCC, part of the neuroendocrine spectrum of lung cancer.

Previous studies have reported poor outcomes for patients with LCNEC, with 5-year survival rates ranging from 15% to 57%.[7,8,20,23]

Therefore, the prognosis of LCNEC patients has not changed. One of the main problems in the definition of the correct therapy is the lack of large phase II and III trials, which are very difficult to design and conduct because of the rarity of this tumor and the difficulties in the diagnosis. A way to overcome this issue may be the creation of large cooperative groups, which can accumulate enough patients to study LCNEC prospectively.

Current standard treatment for early-stage patients is radical surgery. Adjuvant chemotherapy, even in stage I patients, has shown benefit although the optimal schedule is yet to define.[28,48] Neoadjuvant platinum-based regimens may be a feasible option for potentially resectable tumors.[37] Rossi et al.[41] recently demonstrated the efficacy of cisplatin plus etoposide in the adjuvant setting. Nevertheless, all these studies are retrospective.

Observation of clinical behavior and several genetic studies[69,70] showed that LCNEC is very similar to SCLC. Furthermore, Filosso et al.[71] reported preliminary data on the role of octreotide as from adjuvant therapy in LCNEC of the lung.

Irinotecan plus cisplatin combination was shown to be acceptable and feasible as adjuvant chemotherapy for completely resected HGNEC.[37] Thus, a randomized phase III trial is ongoing in Japan to evaluate this combination in comparison with etoposide and cisplatin, for completely resected HGNEC (Japan Clinical Oncology Group 1205/1206).

In the advanced disease setting, the RR to cisplatin-based combinations chemotherapy was 50% in a series of 20 patients.[72] Therefore, it is possible that a first-line NSCLC-like regimen should not be significantly inferior to an SCLC-like regimen.

Some reports showed the presence of EGFR-activating mutations in patients with pulmonary mixed LCNEC.[60,63] It is common evidence that EGFR-TKIs are efficacious in tumors harboring an EGFR-activating mutation regardless of histology. However, these mutations seem to be extremely rare in LCNEC-pure type, whereas they could be identified in the variant with adenomatous component.

Prophylactic cranial irradiation is a useful treatment modality for SCLC,[73] but its role in LCNEC should be an object of future research.

In conclusion, given the rarity of the neoplasm in object and the difficulty in obtaining a reliable diagnosis, especially on small biopsies, it is hopeful to create a cooperation between different hospitals to discuss diagnosis and treatment strategies and to conduct prospective randomized trials, with a number as larger as possible of patients.

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