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Clinical characteristics and treatment management of combined large cell neuroendocrine carcinoma, a subtype of large cell neuroendocrine carcinoma

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Combined large cell neuroendocrine carcinoma (CLCNEC) is a rare neuroendocrine carcinoma, accounting for approximately 10% of large cell neuroendocrine carcinoma (LCNEC). Mainly composed of coexisting adenocarcinoma components, with strong invasiveness and poor prognosis. The treatment regimen for CLCNEC mainly refers to complete surgical resection as the first choice in the early stage, while patients with stage II or higher require adjuvant treatment. At present, research on CLCNEC is mostly small sample and retrospective, and there is no consensus on whether molecular typing and treatment should be carried out. There is considerable controversy over whether it should be managed as small-cell lung cancer (SCLC) or non-small-cell lung cancer (NSCLC). Therefore, in order to solve the problem of confusion in the selection of treatment regimens for CLCNEC, while also considering the therapeutic effects, this article summarizes and analyzes previous studies, fully seeks evidence, and boldly proposes new therapeutic insights: the etoposide-platinum (EP) regimen serves as the basis for adjuvant therapy; In addition, SCLC/NSCLC-CLCNEC can be distinguished based on presence of RB1 and TP53 co-mutation, and targeted therapy or NSCLC type chemotherapy including platinum + gemcitabine or taxanes (NSCLC-GEM/TAX) can be used in combination or sequentially for NSCLC-CLCNEC.

KEYWORDS

combined large cell neuroendocrine carcinoma, LCNEC, molecular typing, RB1 and TP53 co-mutation, adjuvant chemotherapy

1 Rare and uncontrollable CLCNEC

Lung large cell neuroendocrine carcinoma is a relatively rare cancer with high metastasis rate and short survival period, accounting for about 3% of all lung cancers (1–3). International Agency for Research on Cancer (IARC) classification of Thoracic Tumors (5th Edition) published in 2021 classified pulmonary combined large cell neuroendocrine carcinoma (CLCNEC) as a subtype of LCNEC associated with LCNEC components and epithelial components such as adenocarcinoma or squamous carcinoma. In practice, >10% of LCNEC patients are diagnosed with combined LCNEC (CLCNEC) (4, 5). According to reports, CLCNEC is more aggressive and has a poorer prognosis than LCNEC (6, 7). At present, there are relatively few case reports and small-scale retrospective studies on CLCNEC. The main research still analyzes all components as a whole, without distinguishing between pure or combination components (8, 9). According to previous studies, the incidence of CLCNEC is related to males, middle-aged and elderly individuals, and severe smoking (8). The main symptoms include cough, expectoration, chest pain, hemoptysis, and dyspnea (10). The most common mixed component in CLCNEC is adenocarcinoma (AD), accounting for about 70%, followed by squamous cell carcinoma (SCC), accounting for 20% (6, 11). A study suggests that adenocarcinomas-LCNEC is more common in young non-smokers, with lesions typically peripherally located and accompanied by driver gene mutations. Squamous-LCNEC is more common in male patients aged 65 and above, and the lesion is close to the hilum of the lungs. In addition, there is no significant difference between disease-free survival (DFS) and overall survival (OS) between the two CLCNEC subtypes (12).

2 Accurate and precise diagnosis is the foundation of CLCNEC treatment

Travis et al. first uncovered LCNEC as a distinct subtype with neuroendocrine (NE) differentiation but different morphological features compared to small cell lung cancer (SCLC) (13). The pathological manifestations of LCNEC part are complex and varied, and accurate diagnosis requires observation of cell and tissue morphology through light microscopy, combined with immunohistochemical (IHC) features and neuroendocrine particles under electron microscopy. The pathological diagnostic criterion for LCNEC classified by WHO in 2021 are as follows: 1) neuroendocrine morphology with organoid nesting, palisading, rosette-like structures and granular chromatin; 2) High mitotic rate >10 mitoses per 2 mm2 (average 60–80 mitoses per 2 mm2); 3) abundant necrotic tissue; 4) NSCLC cytological features; 5) Positive immunohistochemistry for at least one neuroendocrine marker such as chromograninA(CgA), synaptophysin (Syn), neural cell adhesion molecule 1 (NCAM1/CD56) or NSE, or electron microscopy (14–17). However, the diagnosis of LCNEC is difficult on small biopsy or cytological samples, and immunohistochemistry requires the use of at least two sets of neuroendocrine markers, while CLCNEC is more prone to misdiagnosis due to the presence of other mixed components (18–20).

Researches (11, 12) have found that tumor cells are arranged in a palisade like or chrysanthemum like cluster in the part of CLCNEC, with prominent nuclei and multinucleate division, which is generally consistent with LCNEC. CLCNEC also has epithelial-derived IHC markers corresponding to the expression of focal adenocarcinoma and squamous cell carcinoma components. For example, adenocarcinoma expresses NapsinA, while squamous cell carcinoma expresses CK5/6, p40, and p63. Therefore, apart from meeting the pathologic diagnostic criteria for LCNEC, the diagnosis of CLCNEC also requires the components of adenocarcinoma, squamous cell carcinoma, giant cell carcinoma, and/or spindle cell carcinoma (16, 21). CLCNEC was classified as a subtype of LCNEC in the 2021 WHO Classification of Thoracic Tumours (15), belonging to a different family from NSCLC with NE features such as carcinoid tumor (16). Pathologically these tumors are primarily distinguished based on the mitotic counts, presence or absence of necrosis, and cytologic features (16). Typical carcinoids (TC) show < 2 mitoses per 2 mm2 and absence of necrosis, while atypical carcinoids (AC) show 2 - 10 mitoses and/or punctate foci of necrosis (15). LCNEC has a mitotic count exceeding 10 per 2 mm2, and the degree of necrosis and cellular atypia is much greater than that of that of carcinoid tumors (22). And, the necrosis of LCNEC is common and often represents extensive necrosis (23). Ki-67 staining shows a low proliferation rate in TC, usually less than 5% while in AC it is higher, usually between 5% and 20% (16). Patients with LCNEC have a higher Ki-67 index than those with TC and AC (24), with over 30% usually indicating LCNEC (25–28). At present, routine pathological examination of surgical specimens is an unquestionable diagnostic method for LCNEC, and the proposal of molecular typing can aid in diagnosis and also help discover any potential combination components (15, 18).

3 Molecular characteristics are the "wind vane" of CLCNEC treatment

Genomically, LCNEC is known to share frequent alterations in RB1 and TP53 with SCLC, although different frequencies are reported (4, 29–34). This also indicates that LCNEC has the same TP53 and RB1 mutations as SCLC at the individual gene level, of course, the frequency of RB1 mutations in the LCNEC is lower than that in SCLC (4). Some studies have also mentioned that high-level LCNEC and SCLC exhibit similarity in genome maps (4), with SCLC-like LCNEC having a higher Ki-67 rate and a closer morphological feature spectrum to SCLC than nsclc-like LCNEC (29). Milione et al. reported that LCNECs with co-mutation of TP53 and RB1 (SCLC-like) were significantly enriched in cases with a Ki-67 ≧55%, while the tumors with KRAS mutations were enriched in

Abbreviations: CLCNEC, Combined large cell neuroendocrine carcinoma; LCNEC, Large cell neuroendocrine carcinoma; SCLC, Small-cell lung cancer; NSCLC, Non-small-cell lung cancer; EP, Etoposide-platinum; GEX, gemcitabine; TAX, Taxanes; AD, Adenocarcinoma; SCC, squamous cell carcinoma; DFS, Disease-free survival; OS, Overall survival; ORR, Objective response rate; NE, neuroendocrine; TC, Typical carcinoids; AC, atypical carcinoids; NGS, Next-generation sequencing; TKI, tyrosine kinase inhibitor.

cases with Ki-67 <55% (35). These also confirms that LCNEC has a mixed genome and transcriptome profile, and a therapeutic strategy targeting only one tumor component may be ineffective (36).

In a next-generation sequencing (NGS) analysis of LCNEC, Rekhtman and colleagues identified two major molecular subgroups and one minor subgroup. The major subgroups include co-mutation/loss of TP53 and RB1 and other SCLC-type alterations, including SCLC-like LCNEC with MYC amplification, and NSCLC-like LCNEC lacking simultaneous TP53 and RB1 alterations and almost ubiquitous NSCLC-type mutations (SKT11, KRAS, and/or KEAP1) (29). In George's research, it was also found that LCNECs are composed of two mutually exclusive subgroups - Type I with STK11/KEAP1 alterations and Type II with RB1 alterations (31). In addition, Lazaro and colleagues (37), as well as Simbolo et al. (38), have demonstrated the importance of distinguishing RB1 mutations for the development of LCNEC. At present, the co mutation of TP53 and RB1 may be an important marker for distinguishing between SCLC like and NSCLC like LCNEC, and provide a basis for subsequent treatment.

CLCNEC is a subtype of LCNEC and therefore has its molecular characteristics. Due to the presence of NSCLC part in CLCNEC, the probability of driver gene mutations is higher compared to LCNEC (4, 39). Wang Y et al. (11) conducted NGS analysis on 70 CLCNEC patients who underwent adjuvant chemotherapy after surgery and found that there were 18 patients with EGFR mutation and 4 patients with anaplastic lymphoma kinase (ALK) mutation. Yang Z et al. (12) analyzed 60 CLCNEC resected samples and found 17 patients with EGFR mutation, 4 patients with ALK rearrangement and 2 patients with KRAS mutation. In Simbolo et al.'s (36) study, the probability of KRAS mutation reached 27.8%. In another study (4), 5 out of 10 CLCNEC patients were found to have driver gene alterations. A few studies have also discovered that some CLCNEC patients have rare driver gene mutations, with an EGFR mutation rate of 8.33% and an ALK rearrangement rate of 5.77% (5). In addition, EGFR mutation, BRAF V600E mutation and KIF5B/RET fusion mutation have also been reported in cases of CLCNEC (40–42). Patients with driver gene mutations in CLCNEC were identified through NGS analysis, while some studies did not conduct NGS analysis on the majority of patients (11, 12). In the era of precision medicine, the application of NGS analysis in CLCNEC should be expanded, which can not only distinguish between SCLC like and Nsclc like CLCNEC, but also benefit patients with driver gene mutations from targeted therapy.

4 Specific treatment measures for CLCNEC

In recent decades, the treatment of LCNEC has been more inclined to use non-small cell lung cancer (NSCLC) regimens including cisplatin or SCLC based regimens (3, 43), which are also recommended by the guidelines of the American Society of Clinical Oncology (44). However, the treatment effect and disease remission rate are not satisfactory. For early-stage resectable LCNEC patients, surgical treatment is the primary choice, and lobectomy or pneumonectomy with a systematic nodal dissection can prolong survival (45). Retrospective studies have shown that surgical treatment can achieve satisfactory results to other NSCLC in the early stages of the tumor, and the perioperative mortality rate is also lower (46). However, the 5-year survival rate of stage III LCNEC patients is less than 30%, and the presence of lymph node metastasis is closely related to poor 5-year survival rate (47). Therefore, radical surgery is recommended, but it seems insufficient for the treatment of resectable LCNEC (48–50). Some small sample retrospective studies have shown that perioperative chemotherapy has been shown to bring survival benefits to LCNEC patients. There is controversy over whether to undergo perioperative chemotherapy for resectable stage I LCNEC (51–54), while patients with stage II or higher LCNEC (including CLCNEC) are clearly benefiting from adjuvant chemotherapy (12, 55). For the selection of perioperative chemotherapy regimen, platinum-based adjuvant chemotherapy is superior to non platinum adjuvant chemotherapy (48, 54, 56, 57), and the specific chemotherapy regimen should also be personalized based on molecular typing results.

5 EP regimen chemotherapy as the basis for CLCNEC as adjuvant therapy

In 2005, Rossi et al. convincingly demonstrated for the first time that the use of SCLC-based standard regimens as adjuvant chemotherapy for LCNEC patients is effective and significantly improves survival rates (3). In subsequent studies, chemotherapy regimens similar to SCLC have shown significant efficacy in treating LCNEC patients (57–59), with a clinical response rate of up to 70% (60, 61). Zhuo M et al. (62) demonstrated that the use of the etoposide-platinum regimen has advantages in treating SCLC-like LCNEC patients compared to the pemetrexed-platinum and gemcitabine/taxane-platinum-platinum regimens.The research results of Wang et al. (63) also support the viewpoint of Zhuo et al. (62) They divided 12 patients into a consistent group (NSCLC-like LCENC (n=4) treated with NSCLC-based treatment or SCLC-like LCNEC (n=8) treated with SCLC-based treatment) and an inconsistent group based on molecular subtypes. The conclusion shows that the OS of the consistent group is significantly longer than that of the inconsistent group (median 37.7 vs. 8.3 months; p=0.046). Shen YC et al. also presented that etoposide-platinum doublets acted as an independent prognostic factor for OS (5).

Recent clinical studies have reported that the prognosis of LCNEC receiving SCLC chemotherapy regimen is more effective than NSCLC (3, 57, 58, 64), whether it is in patients with pure LCNEC or CLCNEC (12). CLCNEC should be managed in a multidisciplinary setting, confirming the adjuvant chemotherapy (especially the SCLC regimen) paramount importance to improve patients' outcome (65). A study specifically targeting patients with surgically resectable LCNEC combined with AD and LCNEC combined with SCC included 96 patients (12). Among 78 patients who received 4 cycles of adjuvant chemotherapy, 35 received etoposide based SCLC regimen, and 43 received NSCLC regimen, including pemetrexed, gemcitabine, taxanes and vinorelbine, with

or without platinum. The results showed that the DFS and OS of stage II/III patients who chose the SCLC regimen were better than those who chose the NSCLC regimen. This indicates that CLCNEC patients should still receive basic treatment as neuroendocrine carcinoma patients.This was a specialized study on resectable CLCNEC. Although few patients in their cohort received NGS, it also suggests that all CLCNEC patients should be treated as neuroendocrine cancer patients.

6 NSCLC like CLCNEC should be treated with both NSCLC like regimens. (EP plus NSCLC GEM/TAX)

The SCLC-like subset exhibits SCLC-like morphology characterized by RB1+TP53 coalteration and responds to SCLC chemotherapy regimens, while the nsclc like subset does not. The molecular subtype classification reflected the heterogeneity of pulmonary LCNEC, which might lead to complex chemotherapy efficacy reported by previous studies, as different subtypes might predispose the patients to show different therapeutic response (66, 67). Two single-arm phase II trials in LCNEC (n=29 and n=30) showed an objective response rate (ORR) for etoposide or irinotecan combined with cisplatin ranging from 31% to 47% (58, 64), substantially lower compared to SCLC phase III trials evaluating etoposide-cisplatinum chemotherapy (ORR ≈66%) (68). A recent study was suggested that there is an increase in overall survival (OS) in advanced LCNEC patients when NSCLC regimens are adopted, especially gemcitabine-platinum rather than pemetrexed-platinum (media 7.8 vs. 5.9 months; p=0.019) and etoposide–platinum (SCLC regimens) (media 7.8 vs. 6.7 months; p=0.035) (69). In addition, an evaluation of 26 LCNEC patients showed a significantly lower overall survival for platinum–etoposide chemotherapy compared to a combination of NSCLC regimens (70). After dividing LCNEC subgroups through molecular typing, studies have also found that wild-type RB1 patients who received NSCLC-GEM/TAX treatment had significantly longer OS than those who received SCLC-PE treatment (30). This requires us to particularly consider LCNEC molecular subtypes when selecting treatment options, distinguishing NSCLC subgroups for targeted therapy or other NSCLC-based therapies. Some cases of LCNEC carrying EGFR gene activation mutations have been reported to have good efficacy against EGFR-tyrosine kinase inhibitors (TKIs) (71–75), and ALK inhibitors have also been effective in treating LCNEC cases carrying ALK rearrangements (76). Due to its NSCLC part, driver mutations are more frequent in C-LCNEC compared to pure LCNEC (4, 39), making targeted therapy play a more important role in the treatment of CLCNEC.In Wang Y et al.'s study (11), a total of 9 CLCNEC patients who developed distant metastasis after surgery received TKI treatment. Among them, 5 patients with EGFR 19del/L858R mutation and 4 patients with ALK mutation had an ORR of 66.7%. In Yang Z et al.'s study (12), there were also 5 patients with EGFR mutations and 4 patients with ALK rearrangement who received first or second generation EGFR-TKI and crizotinib treatment, respectively. All patients benefited from targeted therapy. Other case reports have found that CLCNEC patients with ALK fusion benefit from treatment with either alectinib or crizotinib (77–80). These data indicate that combination targeted therapy is the most feasible treatment option for CLCNEC patients diagnosed with non-small cell carcinoma components.

For CLCNEC without driver oncogene aberrations, there is no corresponding "molecular targeted" drug for treatment, and the combination of NSCLC-like chemotherapy is currently the available option. Initially, it was confirmed in an *in vitro* study that VP-16 is a compound that is suitable for combination with gemcitabine if used on the right schedule, especially for lung cancer patients (81). The EP regimen of chemotherapy combined with RT followed by a three cycles docetaxel was popularized after the completion of Southwest Oncology Group (SWOG) 9504, which also resulted in the optimal survival period for stage III NSCLC (82). In recent studies (83, 84), the efficacy of combination chemotherapy for different types of tumors also supports the "hypothesis" - combining multiple, individually effective, chemotherapeutic mechanisms could overcome tumor heterogeneity, producing longer lasting remissions in more patients, and perhaps even cures (85, 86).

Recently, in Wang's study (87), NSCLC-like (without TP53/RB1 co-alterations) LCNEC patients were also attempted to receive NSCLC plus SCLC chemotherapy regimen. Although there is a lack of prospective research, combined NSCLC-based regimens is necessary for CLCNEC patients with non small cell carcinoma components when there is no driver mutation.

7 Radiotherapy and immunotherapy for CLCNEC are still being explored

There are few studies on radiotherapy for LCNEC patients. Some studies have shown that radiotherapy has potential benefits in improving the survival of non metastatic LCNEC patients (88), while others have shown that radiotherapy significantly improves the overall survival of stage III patients (89). Prelaj et al. found in their study of 28 patients with stage III-IV LCNEC who received chest radiotherapy and prophylactic cranial irradiation (PCI) that both mOS and mPFS were higher in patients receiving chest radiotherapy and PCI than those who did not receive treatment (90). In Rieber et al.'s study (91), brain radiotherapy was chosen as the preferred treatment for patients with LCNEC brain metastases.

More exploration is needed to determine whether ICIs can bring benefits to LCNEC patients. In a retrospective study (92), 11 PD-L1 positive LCNEC patients received treatment with nivolumab or pembrolizumab, and 60% of patients achieved partial remission. Dudnik et al. (93) found in their study of advanced LCNEC patients that ICIs can improve both quality of life and mOS. In the study by Oda et al. (94), a patient with multiple postoperative relapses of LCNEC showed a reduction in all metastatic lesions after nivolumab treatment and maintained a partial response for 5 years after surgery. The use of immunotherapy for CLCNEC

patients is currently only a few case reports. Xu et al. (95) reported a case of CLCNEC patient who underwent adjuvant chemotherapy, radiotherapy and maintenance therapy with durvalumab and achieved complete remission. Another elderly male patient with CLCNEC achieved partial response after receiving chemotherapy plus atezolizumab (96).

8 Conclusion

CLCNEC is a relatively rare neuroendocrine carcinoma with strong invasiveness and poor prognosis. Due to the presence of other mixed components, small biopsy or cytological diagnosis is difficult, and routine pathological examination of surgical specimens is an unquestionable diagnostic method. For early-stage resectable LCNEC patients, surgical treatment is the main choice, while patients with stage II or higher CLCNEC require adjuvant treatment. In the era of precision medicine, the application of molecular spectrum analysis in CLCNEC should be expanded, whether it is distinguishing between SCLC like and Nsclc like CLCNEC through TP53 and RB1 co mutations, or searching for oncogene aberrations to perform corresponding molecular targeted therapies. There is sufficient research evidence for LCNEC patients to receive basic treatment as neuroendocrine carcinoma patients. On this basis, we believe that CLCNEC with co mutations of RB1 and TP53 should still be treated with EP regimen chemotherapy for neuroendocrine carcinoma; However, the absence of RB1 and TP53 co mutations in CLCNEC, which is purely treated as neuroendocrine carcinoma, often does not benefit patients due to the dominance of its non small cell carcinoma components, requiring the combination of adjuvant targeted therapy or NSCLC type chemotherapy including NSCLC-GEM/TAX for personalized treatment. Currently, the available studies regarding CLCNEC treatment lacks authority, and further research is needed to design larger prospective studies to confirm the effectiveness of distinguishing the components of CLCNEC for treatment. We will be committed to such studies.

Author contributions

KK: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. SW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. BL: Formal analysis, Investigation, Writing – original draft. JW: Investigation, Writing – original draft. XL: Conceptualization, Formal analysis, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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