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Multicentre phase II study of cisplatin–etoposide chemotherapy for advanced large-cell neuroendocrine lung carcinoma: the GFPC 0302 study

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Background: The optimal treatment of large-cell neuroendocrine carcinoma (LCNEC) of the lung remains unclear. Here, our primary objective was to assess the efficacy of cisplatin–etoposide doublet chemotherapy in advanced LCNEC. Accuracy of the pathological diagnosis and treatment toxicity were assessed as secondary objectives.
Patients and methods: Prospective, multicentre, single-arm, phase II study with a centralised review of treatment-response and pathological data. Patients had untreated performance status (PS) 0/1 stage IV/IIIB LCNEC and received cisplatin (80 mg/m22 d1) and etoposide (100 mg/m22 d1-3) every 21 days.
Results: Eighteen centres included 42 patients (mean age, 59 ± 9 years; 69% men; median of four cycles/patient). At least one grade-3/4 toxicity occurred in 59% of patients (neutropaenia, thrombocytopaenia, and anaemia in 32%, 17%, and 12%, respectively). The median progression-free survival (PFS) and overall survival (OS) were 5.2 months (95% confidence interval, CI, 3.1–6.6) and 7.7 months (95% CI, 6.0–9.6), respectively. The centralised pathologist review reclassified 11 of 40 (27.5%) patients: 9 as small-cell lung cancer, 1 as undifferentiated non-small-cell lung cancer, and 1 as atypical carcinoid. Survival data were not significantly changed by excluding the reclassified patients.
Conclusions: The pathological diagnosis of LCNEC is difficult. The outcomes of advanced LCNEC treated with cisplatin–etoposide doublets are poor, similar to those of patients with advanced small-cell lung carcinoma (SCLC).
Key words: carcinoma, clinical trial phase II, large cell neuroendocrine tumours, small-cell lung cancer

introduction

Large-cell neuroendocrine carcinoma (LCNEC) of the lung accounts for no more than 1% of all lung cancers. The typical histological features, first described in 1991 [1, 2], include large cells with abundant cytoplasm, a high mitotic rate, extensive necrosis, and a neuroendocrine growth pattern. The World Health Organisation currently classifies LCNEC as a distinct subtype of pulmonary large-cell carcinoma [3] and, therefore, as a subtype of non-small-cell lung carcinoma (NSCLC). However, LCNEC lacks the specific histologic features of NSCLC such as glandular or squamous differentiation, but instead displays evidence of neuroendocrine differentiation reminiscent of small-cell lung carcinoma (SCLC), although the malignant cells in SCLC are smaller, with scant cytoplasm, and invade the tissues in sheets. LCNECLCNEC shares genetic alterations with SCLC [4]. The higher mitotic rates and more extensive necrosis seen in LCNEC and SCLC are in contrast to the lower-grade neuroendocrine tumours, i.e. typical and atypical carcinoids. LCNEC and SCLC also share clinical characteristics including a preponderance of males and smokers and an aggressive clinical course [5–9]. The clinical outcome of LCNEC patients is poor, with overall 5-year survival rates ranging from 15% to 57%. Studies have demonstrated significantly worse survival in LCNEC compared with other non-small-cell carcinomas but not compared with SCLC [9].

In terms of treatment, several recent studies have shown that LCNEC responds to cisplatin-based chemotherapeutic regimens similar to those used for SCLC [9]. However, these are retrospective studies in small numbers of patients [9–11] and consequently the sensitivity of LCNEC to the chemotherapeutic regimens commonly used for SCLC remains unclear [12].

Here, our primary objective was to assess the efficacy of cisplatin–etoposide doublet chemotherapy in patients with advanced LCNEC. Secondary objectives were to assess the

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accuracy of the pathologic diagnosis of LCNEC and to evaluate the toxic effects of cisplatin–etoposide doublet chemotherapy.

methods

This prospective, multicentre, single-arm, phase II trial was approved by the appropriate ethics committee (Marseille 2, Number 03/71). A written informed consent was obtained from each patient before study inclusion.

The study patients were recruited at 18 study centres in France between May 2004 and December 2009. Patients were eligible if they had histologically documented LCNEC meeting criteria for stage IV disease or for stage IIIB disease with pleural involvement. Pathological definition of LCNEC was as previously described [3] cohesive sheet of large tumoural cells with an endocrine pattern, often one or several nucleoli and expression of at least two out of the three neuroendocrine markers; CD56, synaptophysin and chromogranin.The other inclusion criteria were as follows: performance status (PS) 0/1; age 18–75 years; no previous chemotherapy; measurable target in a non-irradiated region; absence of peripheral neuropathy grade 2 or higher; life expectancy more than 3 months, and biological status compatible with chemotherapy (bilirubin <1.25 ULN, transaminase activity <3 ULN, alkaline phosphatase <2.5 ULN, polymorphonuclear neutrophil count >1.5 G/l, and platelet count >100 G/l). Patients with a history of palliative radiation therapy could be included. We did not include patients with mixed histological features or a diagnosis of LCNEC established only by cytological examination. The other no inclusion criteria were histological status (small-cell lung cancer, bronchioloalveolar carcinoma), prior chemotherapy, symptomatic brain metastases, unstable heart disease, uncontrolled infection, grade >2 neuropathy and a history of metastatic malignancy in the last 5 years.

Chemotherapy consisted of cisplatin, 80 mg/m^2, as a 30-min intravenous infusion on day 1 (D1) and etoposide, 100 mg/m^2 on D1, D2, and D3. This combination was given at 21-day intervals, up to six times. Growth-factor therapy was at the discretion of the investigator in charge of patient care. A clinical evaluation and laboratory tests were carried out at the beginning of each cycle.

The primary end point was the objective response rate. Responses were evaluated based on Response Evaluation Criteria in Solid Tumours (version 1.0), after three and six treatment cycles. Computed tomography or magnetic resonance imaging was used for radiologically measurable tumours. All imaging studies and TNM classifications were subjected to a centralised review. A panel of six pathologists carried out a centralised review of all histological specimens; they worked, independently with differences resolved by consensus; patients who were reclassified as having tumours other than LCNEC continued their participation in the study. Toxic effects were recorded and graded according to the National Cancer Institute Common Toxicity Criteria (AE version 3.0).

statistical analysis

In this exploratory open phase II study, the hypothesis was to reject platin doublet if the disease control rate (RR) was lower than 30% and retain this doublet for an RR higher than 50% (risk alpha 5%, statistical power 80%); two analysis were planned after 20 and after 35 inclusions and the protocol had to be stopped for futility if there were respectively less than three and less than six patients with disease control; the planned number of patients was 42.

Quantitative data were described as median and range and qualitative data as percentage. Groups were compared using the chi-square test.

Efficacy was assessed per patient. The objective response rate was computed in the intention-to-treat population as the number of responders over the total number of study patients. Treatment discontinuation due to toxicity was classified as treatment failure. We also computed the objective response rate as the number of responders over the number of patients who could be evaluated at the sixth cycle. Finally, we computed the objective response rate based on the best radiological response observed during the six cycles. For all response rates, the 95% confidence intervals (95% CIs) were computed.

Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method from baseline to the date of radiological progression or death for PFS, date for death for OS. For patients alive at last follow-up, the data were censored at the last follow-up visit. The median follow-up was estimated using the inverse Kaplan–Meier method. The analysis was based on a data cut-off date of April 2012.

results

The 18 study centres enrolled 42 patients during the study period. The mean age was 59 ± 9 years (range 33–73 years) and 29 (69%) patients were men (Table 1). The mean time from diagnosis to study inclusion was 0.9 ± 1.2 months.

Tumour stage was IV in 88% of patients (Table 1). The centralised pathology review was possible for 40 (95%) patients and led to the reclassification of 11 (27.5%) patients into the following diagnostic categories: SCLC, $n = 9$; undifferentiated NSCLC, $n = 1$; and atypical carcinoid, $n = 1$.

In the intention-to-treat analysis of the overall population, stabilisation occurred in 26% of patients, a partial response in 38%; the study meet is the primary end point with a 64% disease control rate. When we confined the analysis to the 29 patients in whom the diagnosis of LCNEC was confirmed by the centralised pathology review, the rates of stabilisation, partial response, and disease progression were 31%, 34%, and 35%, respectively; these proportions were not significantly different from those in the overall population ($P = 0.18$).

The median follow-up was 37.2 months. The median PFS in the overall population was 5.2 months (95% CI, 3.1–6.6 months) and the median OS was 7.7 months (95% CI, 6.0–9.6 months) as shown by Figure 1. After 1 year, the PFS rate was 14.3% (95% CI, 6.7–27.8) and the OS rate was 26.8% (95% CI, 15.7–41.9). In the analysis confined to the patients with confirmed LCNEC, the median PFS was 5.0 months (95% CI,

Table 1. Main characteristics of the 42 study patients

Characteristics	$n = 42$
Age in years, mean ± SD (range)	59 ± 9 (33–73)
Sex, *n* (%) of males	29 (69%)
Weight loss, %, mean ± SD (range)	5.9% ± 7% (0–29)
Performance status, PS, *n* (%)	
0	16 (48%)
1	22 (52%)
Stage	
IV metastatic	37 (88%)
IIIB with pleural T4	5 (12%)
Cisplatin–etoposide chemotherapy given, *n*	41
Number of cycles, median	4
Cisplatin dose in mg, median	520
Etoposide dose in mg, median	1740

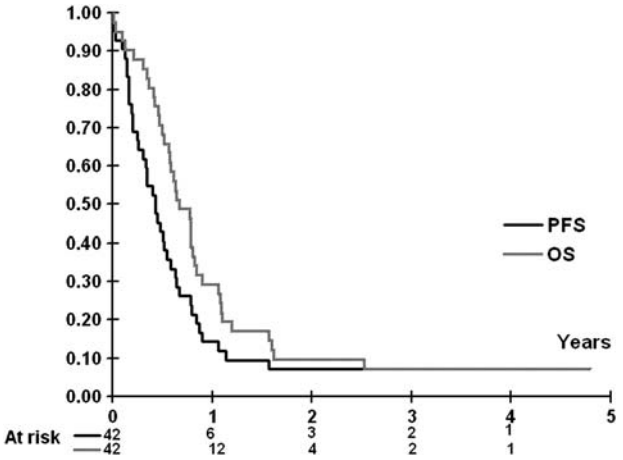

Figure 1. Progression-free survival (PFS) and overall survival (OS) in the intention-to-treat population.

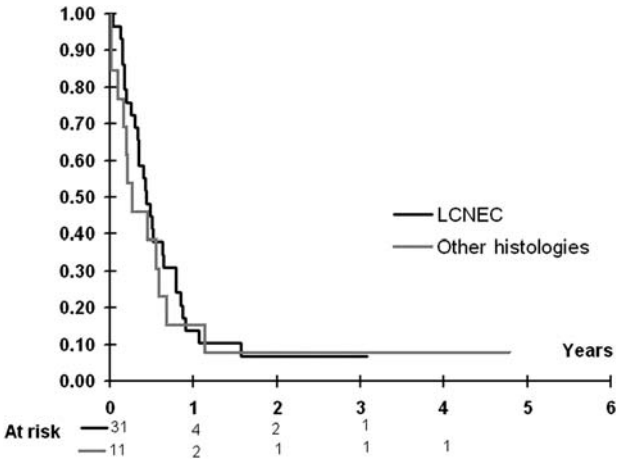

Figure 2. Progression-free survival (PFS) according to the histological diagnosis after a centralised pathology review of 40 (95%) patients; 11 patients were reclassified into the following diagnostic categories: SCLC, $n = 9$; undifferentiated NSCLC, $n = 1$; and atypical carcinoid, $n = 1$).

4.0–7.9) and the median OS was 8.0 months (95% CI, 3.7–7.9); the corresponding figures in the 11 patients with diagnoses other than LCNEC were 3.1 months (95% CI, 2.8–8.5) and 7.0 months (95% CI, 3.0–9.0), respectively, with no significant differences compared with the LCNEC group ($P = 0.55$), as shown by Figure 2.

At least one chemotherapy cycle was given to 41 (98%) patients, and the median number of cycles was four per patient (Table 2). At least one chemotherapy cycle was postponed because of leukopaenia/neutropaenia in 23 (56%) patients and at least one dosage reduction was required in 9 (22%) patients. At least one grade-3/4 toxicity occurred in 59% of patients; the main grade-3/4 toxic effects were neutropaenia, thrombocytopaenia, and anaemia (32%, 17%, and 12% of patients, respectively, Table 2). Reasons for chemotherapy discontinuation were disease progression (38%), completion of the six cycles (32%), toxicity (20%), and death (10%).

Table 2. Toxicity rates seen in over 10% of the patients and rates of grade-3/4 toxic effects

	Any grade, *n* (%)	Grade 3/4, *n* (%)
At least one toxicity	39 (95)	24 (59)
Anaemia	29 (71)	5 (12)
Neutrophils	24 (59)	13 (32)
Vomiting	19 (46)	3 (7)
Asthenia	15 (37)	1 (2)
Thrombocytopaenia	13 (32)	7 (17)
Alopecia	12 (29)	1 (2)
Nausea	9 (22)	1 (2)
Renal toxicity	9 (22)	2 (5)
Decline in general health	8 (20)	5 (12)
Pain	7 (17)	1 (2)
Constipation	5 (12)	0
Fever	5 (12)	0
Neurological disorders	5 (12)	1 (2)

discussion

In this prospective, multicentre study of patients with advanced LCNEC, cisplatin–etoposide doublet chemotherapy provided median PFS and OS durations of 5.2 and 7.7 months, respectively. The centralised pathology review showed that the histological diagnosis of LCNEC was difficult, as it led to reclassification of one-fourth of the patients. To our knowledge, our study is among the largest prospective studies of advanced LCNEC. No studies have established the optimal treatment for patients with LCNEC. More specifically, whether chemotherapy protocols designed for NSCLC or SCLC may benefit patients with LCNEC remains unknown.

A recent retrospective review of 45 consecutive patients with advanced LCNEC assessed the outcomes depending on whether first-line chemotherapy used regimens designed for SCLC ($n = 11$) or for NSCLC ($n = 34$) [9]. The response rates in these two groups were 73% and 50%, respectively ($P = 0.19$), the median PFS durations were 6.1 and 4.9 months ($P = 0.41$), and the median OS durations were 16.5 and 9.2 months ($P = 0.10$). The type and efficacy of salvage chemotherapeutic regimens differed considerably between the two groups: salvage regimens including irinotecan, platinum, or taxanes, commonly used in the SCLC-regimen group, provided relatively high objective response rates; whereas the frequently used salvage agents in the NSCLC-regimen group, such as pemetrexed, gefitinib, and erlotinib, failed to induce objective responses. A small retrospective review of 12 patients with LCNEC [13] provided support for the therapeutic approach used in SCLC, i.e. cisplatin–etoposide chemotherapy with or without radiotherapy, which produced partial or complete responses. Another retrospective study [14] enrolled 22 patients with measurable LCNEC, including 15 with stage IV disease. Chemotherapy consisted of cisplatin and irinotecan ($n = 9$), a platinum agent and paclitaxel (Taxol, $n = 6$), paclitaxel alone ($n = 1$), cisplatin and vinorelbine ($n = 1$), cisplatin and docetaxel ($n = 1$), or platinum and etoposide ($n = 4$). The objective response rate was 59.1% and the median PFS and OS were 4.1 and 10.3 months, respectively. Finally, in

three retrospective reviews of, respectively, 14, 20 and 25 patients with LCNEC, treated with various chemotherapy regimens LCNEC (the response rate was comparable with that seen in SCLC; however, the samples size of these studies were small, the disease stage varied widely, and in some cases patients had been treated previously [10, 15, 16].

The multicentre design and uniformity of the patient population are major strengths of our study. Cisplatin–etoposide doublet chemotherapy in our patients with LCNEC provided a similar efficacy to that reported in extensive SCLC (median PFS and OS values of 4.8 and 9.4 months in the phase III trial comparing cisplatin–etoposide with cisplatin–irinotecan and a median OS value of 8.4 months in the phase III trial of cisplatin–etoposide versus cyclophosphamide–epirubicin–vincristine triplet chemotherapy), [17, 18]. The behaviour of advanced LCNEC seems to be similar to that of extensive SCLC, and none of the results from our study suggest a less favourable prognosis [19].

Another major strength of our study is the centralised review of the histology specimens by a panel of pathologists. LCNEC is a poorly recognised and underdiagnosed entity that is frequently mistaken for poorly differentiated NSCLC, atypical carcinoid tumours, or intermediate cell-type SCLC. This centralised review led to the reclassification of 27.5% of the patients, usually as having SCLC. Similarly, in another study [20] only 53% ($n = 44$) patients were originally correctly classified as having LCNEC, whereas 47% were misdiagnosed as having NSCLC. These diagnostic errors are chiefly ascribable to the difficulty in recognizing the neuroendocrine-cell morphology by light microscopy, especially in cytology samples or small biopsy specimens.

In conclusion, the pathological diagnosis of LCNEC is difficult. The outcomes of advanced LCNEC treated with cisplatin–etoposide doublets are poor, similar to those of patients with advanced SCLC. Further prospective studies on LCNEC are needed to better delineate the prognosis and sensitivity to chemotherapy regimens of this rare malignancy.

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disclosure

The authors have declared no conflicts of interest.

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