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Original Article

Immunotherapy-combined chemotherapy as first-line treatment for stage IIIB/IV large cell neuroendocrine lung carcinoma

Zhuoran Li[1], Zhixiu Xu[2], Luonan Wang[1], Xiaona Mao[1], Tingting Huo[1], Cailing Jin[1]

[1]Department of Oncology, The First Affiliated Hospital of Henan Medical University, Xinxiang Key Laboratory of Diagnosis and Treatment of Thoracic Cancer (Lung and Esophagus), Weihui 453100, Henan, China; [2]Department of Neurology, The First Affiliated Hospital of Henan Medical University, Henan Key Laboratory of Neurorestoratology, Henan Joint International Research Laboratory of Neurorestoratology for Senile Dementia, Henan Key Laboratory of Neurorestoratology, Weihui 453100, Henan, China

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Abstract: Objectives: The optimal first-line treatment for advanced large cell neuroendocrine carcinoma of the lung (LCNEC) remains unclear. This study aimed to comprehensively evaluate and compare the efficacy of different first-line treatment regimens in patients with stage IIIB/IV LCNEC. Methods: A retrospective analysis was performed on 93 patients diagnosed with stage IIIB/IV LCNEC at The First Affiliated Hospital of Henan Medical University from March 2017 to December 2022. Based on the initial therapeutic regimen, patients were divided into three groups: chemotherapy alone (Chemotherapy group, n=55), chemotherapy combined with immunotherapy (Immunotherapy+chemotherapy group, n=23), and epidermal growth factor receptor (EGFR)-targeted therapy (Targeted therapy group, n=15; for EGFR-mutant patients). Efficacy was evaluated using objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Results: The Chemotherapy group had a median PFS of 4.3 months and a median OS of 12.3 months. The Immunotherapy+chemotherapy group achieved an ORR of 56.5% and a DCR of 91.3%, with a significantly longer median PFS of 10.6 months compared to the Chemotherapy group (P<0.0001). The Targeted therapy group showed a median PFS of 6.9 months and a median OS of 18.8 months. Notably, the median PFS of the Immunotherapy+chemotherapy group was markedly prolonged relative to the Chemotherapy group (P<0.0001). Conclusions: Chemotherapy combined with immunotherapy may be a promising first-line treatment strategy for patients with stage IIIB/IV LCNEC, as it significantly improves PFS compared to chemotherapy alone. Additionally, targeted therapy yields encouraging outcomes in EGFR-mutant patients.

Keywords: Large cell neuroendocrine carcinoma, chemotherapy, immunotherapy, targeted therapy

Introduction

Large cell neuroendocrine carcinoma of the lung (LCNEC) is a highly aggressive malignancy, accounting for approximately 3% of all primary lung tumors [1], and it typically confers a poor prognosis [2]. Given the overlapping clinicopathological characteristics between small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), the initial chemotherapy regimen for advanced LCNEC is extrapolated from those used for SCLC or NSCLC [3, 4]. Some studies have suggested that the platinum-gemcitabine regimen-commonly employed in NSCLC-may be more effective than other platinum-based combinations (e.g., platinum-pemetrexed [Pem] and platinum-etoposide) for patients with advanced LCNEC [5]. Conversely, other small-scale prospective and retrospective studies have demonstrated that SCLC-like regimens can yield therapeutic benefits in advanced LCNEC [3, 6-8]. Despite the American Society of Clinical Oncology recommending either SCLC-like or NSCLC-like chemotherapy regimens for advanced LCNEC [9], a consensus on the optimal systemic chemotherapy remains elusive.

Advancements in cancer research have significantly improved our understanding of the roles of chemotherapy combined with immunothera-

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py, immunotherapy alone, and targeted therapy in stage III/IV NSCLC [10-13]. For example, in the ORIENT-11 trial, the combination of sintilimab with pemetrexed and platinum significantly improved overall survival (OS) compared with chemotherapy plus placebo as a first-line regimen for NSCLC [14]. Similarly, recent small-scale cohort and retrospective studies have reported promising antitumor efficacy of immune checkpoint inhibitors (ICIs) in patients with advanced LCNEC [15-18]. However, these studies primarily evaluated ICIs as frontline therapy or salvage therapy following chemotherapy. The ongoing DUPLE clinical trial (EudraCT Number: 2020-005942-41) is investigating durvalumab plus etoposide/carboplatin as first-line treatment for metastatic LCNEC, followed by durvalumab maintenance therapy; this trial may provide further insights into the efficacy of this approach.

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have become the preferred regimen for EGFR-mutant patients with advanced NSCLC [11, 19-21]. However, the anticancer effect of EGFR-TKIs in LCNEC patients has only been discussed in a small number of case studies [22-25]. Due to the lack of definitive evidence supporting specific therapeutic options for stage IIIB/IV LCNEC, standardized clinical management guidelines are currently unavailable. Therefore, establishing an optimal treatment regimen for this aggressive disease is imperative. In the present study, we conducted a retrospective analysis of first-line treatment options for patients with stage IIIB/IV LCNEC, with the aim of providing valuable insights for potential future therapeutic strategies in advanced LCNEC.

Patients and methods

Case selection

This study was conducted at The First Affiliated Hospital of Henan Medical University from March 2017 to December 2022. A total of 93 patients with stage IIIB/IV LCNEC who received treatment were enrolled based on International Classification of Diseases, 9th Edition (ICD-9) codes [26] and histopathological data retrieved from the hospital's medical records. The study was approved by the Institutional Review Board (IRB) of The First Affiliated Hospital of Henan Medical University (Approval No.: EC-023-006). Due to its retrospective nature, written informed consent from individual patients was waived.

Data collection

Patient data were collected from the hospital's medical records. Collected demographic and clinical characteristics included gender, age, smoking history, TNM stage, and programmed death-ligand 1 (PD-L1) expression status. Treatment-related information encompassed the initiation date of first-line treatment, treatment regimen, treatment response, PD-L1 status (determined by immunohistochemical staining of biopsy specimens), driver gene mutations (detected via reverse transcription-polymerase chain reaction [RT-PCR] of biopsy specimens), chemotherapy details, and patient outcomes. Biochemical indicators included preoperative serum tumor marker levels, such as carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), neuron-specific enolase (NSE), and carbohydrate antigen 125 (CA125). Immunoglobulin levels (IgA, IgG, and IgM) were also recorded. All patients were assigned Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) scores ranging from 0 to 3. Primary endpoints were set as treatment response and survival status, while secondary endpoints included biochemical indicators and adverse events.

Intervention methods

Patients were divided into three groups according to their initial first-line treatment regimens: (1) Chemotherapy group (n=55): patients received either SCLC-like chemotherapy regimens (e.g., etoposide/cisplatin [EP], etoposide/carboplatin [EC]) or NSCLC-like chemotherapy regimens (e.g., docetaxel/cisplatin [DP], paclitaxel/cisplatin [TP], paclitaxel/carboplatin [27], pemetrexed/cisplatin [Pem/P], pemetrexed/nedaplatin [Pem/N]). (2) Chemotherapy Combined with Immunotherapy (Immunotherapy+ chemotherapy group, n=23): patients received durvalumab plus EP, sintilimab plus pemetrexed (Pem), or sintilimab plus TC (paclitaxel/carboplatin). (3) Targeted therapy group (n=15): this group included only patients with EGFR mutations, who were treated with EGFR-TKIs such as afatinib, gefitinib, or osimertinib.

Clinical efficacy evaluation and follow-up

Tumor response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors version 1.1 [28]. Objective response rate (ORR) and disease control rate (DCR) were calculated using the following formulas:

$$ORR = \frac{\text{Number of patients with CR} + \text{Number of patients with PR}}{\text{Total number of patients}}$$

$$DCR = \frac{\text{Number of patients with CR} + \text{Number of patients with PR} + \text{Number of patients with SD}}{\text{Total number of patients}}$$

Where CR, PR, and SD represent complete response, partial response, and stable disease, respectively.

Progression-free survival (PFS) was defined as the time from the initiation of first-line treatment to disease progression (PD) or death. Overall survival (OS) was defined as the time from the initiation of first-line treatment to death or the last follow-up. Survival data were collected from hospital inpatient/outpatient medical records and direct follow-up with patients or their family members. The follow-up period ended on December 31, 2022.

Adverse events

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version not specified, graded as I-IV) [29]. Adverse events were evaluated after each cycle of chemotherapy, and the final grade for each patient was determined based on the most severe grade recorded within the 4-week evaluation period.

Quality of life (QoL)

QoL was evaluated using the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale. This scale consists of 36 items across five domains: physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), functional well-being (7 items), and additional lung cancer-specific concerns (9 items). Each item was scored on a 5-point Likert scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much). Positive items were scored directly (0-4), while negative items were reverse-scored (0-4). The total score for each domain was the sum of the scores of its respective items, with higher scores indicating better QoL. QoL assessments were conducted before the first cycle and after the fourth cycle of chemotherapy.

Statistical analysis

All statistical analyses were performed using SPSS software (version 26.0) and GraphPad Prism (version 9). Categorical variables were presented as frequencies and percentages, and comparisons between groups were performed using the chi-square test. Continuous variables with a normal distribution were expressed as mean±standard deviation (SD), and group differences were analyzed using Student's t-test or one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Continuous variables with a non-normal distribution were analyzed using the Mann-Whitney U test. Survival curves were plotted using the Kaplan-Meier method, and differences in PFS and OS between groups were compared using the log-rank test. Univariate analyses were performed to identify variables significantly associated with PFS and OS. A two-tailed *P*-value <0.05 was considered statistically significant.

Results

Comparison of patient characteristics and clinical efficacy

The demographic and clinical characteristics of the patients are presented in **Table 1**. The median age of the cohort was 67 years, with a range of 46-73 years. The cohort included 70 males (75.3%) and 23 females (24.7%). Smoking status was documented in 51 patients (54.8%), and 42 patients (45.2%) were non-smokers. A total of 78 patients (83.9%) had an ECOG PS score of 0-1, which indicates good to moderate functional capacity. There were significant differences in age and gender among the three groups (P<0.05), while there were no significant differences in the other indicators (P>0.05).

The results of clinical efficacy and survival analysis are presented in **Table 1** and **Figure 1**. In the chemotherapy group, 27 patients (49.1%) achieved a PR, 18 patients (32.7%) had SD, and 10 patients (18.0%) had PD. The ORR reached 49.1%, and the DCR was 81.8%. Median PFS (mPFS) was 4.3 months, and median OS (mOS) was 12.3 months. In the Immunotherapy+chemotherapy group, 13 pa-

Table 1. Demographic and clinical outcome of different treatment regimens

Variables	Total (n=93)	Chemotherapy (n=55)	Immunotherapy+chemotherapy group (n=23)	Targeted therapy group (n=15)	X^2/F	*P*-value
Age (years), Median (IQR)	67.0 (59.0, 69.0)	62.0 (54.5, 68.0)	69.0 (65.0, 70.0)	70.0 (67.5, 71.5)	13.530	<0.0001
Gender, n (%)					22.792	<0.0001
Female	23 (24.7)	9 (16.4)	3 (13.0)	11 (73.3)		
Male	70 (75.3)	46 (83.6)	20 (87.0)	4 (36.7)		
Smoke, n (%)					5.915	0.052
No	42 (45.2)	21 (38.2)	10 (43.5)	11 (73.3)		
Yes	51 (54.8)	34 (61.8)	13 (56.5)	4 (36.7)		
PS, n (%)					1.172	0.557
0-1	78 (83.9)	48 (87.3)	18 (78.3)	12 (80.0)		
2-3	15 (16.1)	7 (12.7)	5 (21.7)	3 (20.0)		
Stage [n (%)]					3.369	0.498
IIIB	18 (19.4)	9 (16.4)	5 (21.7)	4 (26.7)		
IVA	32 (34.4)	17 (30.9)	8 (34.8)	7 (46.6)		
IVB	43 (46.2)	29 (52.7)	10 (43.5)	4 (26.7)		
Response, N (%)					7.754	0.101
PR	53 (57.0)	27 (49.1)	13 (56.5)	13 (86.6)		
SD	27 (29.0)	18 (32.7)	8 (34.8)	1 (6.7)		
PD	13 (14.0)	10 (18.2)	2 (8.7)	1 (6.7)		
Cycles (median, IQR)	3.0 (2.0, 6.0)	4.0 (3.0, 6.0)	2.0 (2.0, 6.0)	3.0 (2.0, 7.0)	0.149	0.862
PD-L1 status [n (%)]					2.470	0.650
Positive	28 (30.1)	15 (27.3)	9 (39.1)	4 (26.7)		
Negative	9 (9.7)	4 (7.3)	3 (13.0)	2 (13.3)		
Not detected	56 (60.2)	36 (65.4)	11 (47.8)	9 (60.0)		
PFS (month), Median (IQR)	8.6 (3.6, 10.3)	4.3 (1.9, 9.8)	10.6 (9.5, 14.1)	6.9 (6.0, 9.1)	19.70	<0.0001
OS (month), Median (IQR)	17.1 (6.8, 25.0)	12.3 (2.3, 25.0)	20.8 (9.5, 24.4)	18.8 (12.9, 27.1)		0.039

Abbreviations: IQR, inter quartile range; PR, partial response; SD, stable disease; PD, progressive disease; PS, performance status; PFS, progression free survival; OS, overall survival.

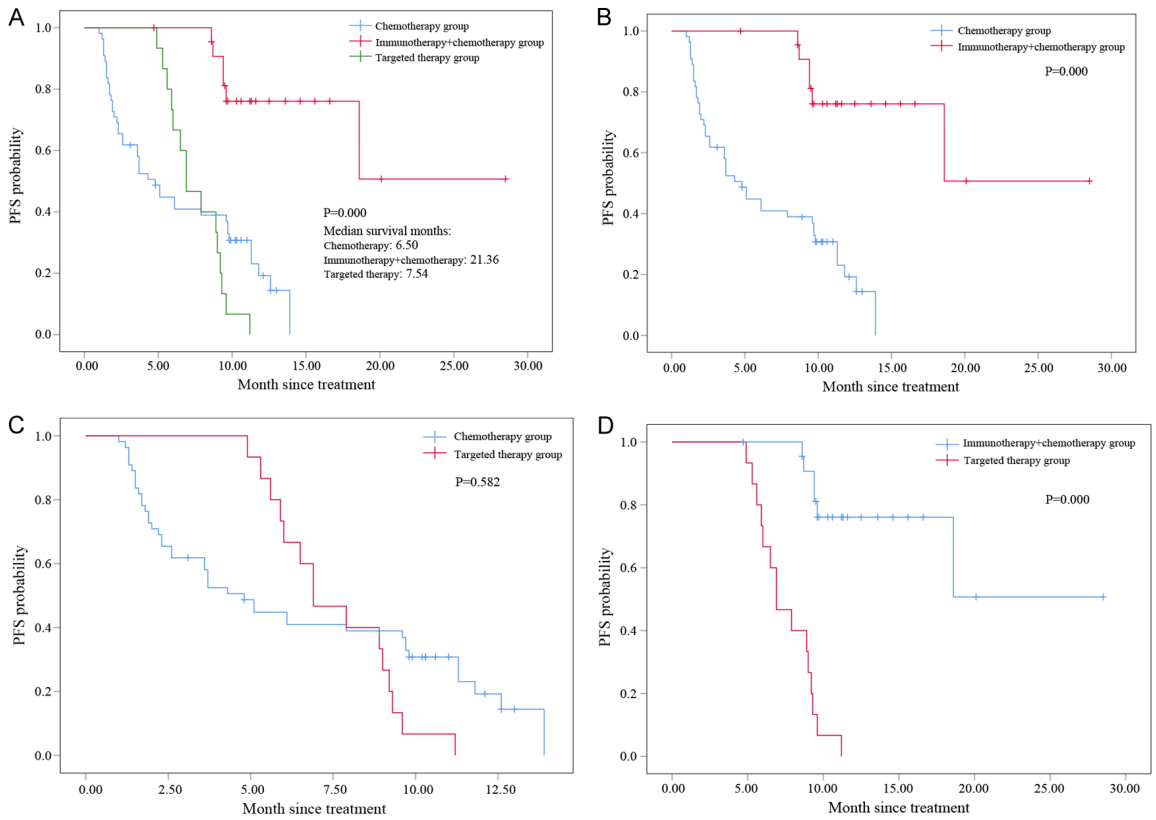

Figure 1. Kaplan-Meier progression-free survival curves for patients with stage IIIB/IV LCNEC receiving different treatment regimens. A: comparison of PFS between three groups (log-rank test, P<0.0001). Median PFS: chemotherapy=6.50 months, Immunotherapy+chemotherapy group=21.36 months, targeted therapy group=7.54 months. B: Comparison of PFS between chemotherapy and Immunotherapy+chemotherapy group (log-rank test, P≤0.0001). C: Comparison of PFS between chemotherapy and targeted therapy group (log-rank test, P=0.582). D: Comparison of PFS between Immunotherapy+chemotherapy group and targeted therapy group (log-rank test, P<0.0001).

tients (56.5%) achieved PR, and 8 patients (34.8%) had SD. The ORR was 56.5%, and the DCR was 91.3% In the targeted therapy group, 13 patients (86.6%) achieved PR while 1 patient had SD (6.7%), resulting in an ORR of 86.6% and DCR of 93.3%. The mPFS was 6.9 months), and the mOS was 18.8 months. There were significant differences in PFS and OS among the three groups (all P<0.05).

Comparison of the impact of various factors on PFS and OS

The impact of various clinical factors on PFS and OS is presented in **Figure 2** and **Table 2**. Age, gender, and smoking status showed no significant correlation with either PFS or OS (all P>0.05). In contrast, treatment regimen was significantly associated with PFS. Specifically, the Immunotherapy+chemotherapy group had a markedly longer PFS than the chemotherapy group (P<0.0001). No significant difference in PFS was observed between the chemotherapy and targeted therapy groups (P=0.546). A similar trend was observed for OS, with no significant differences in OS among the three treatment groups, following the same comparison pattern (P>0.05).

Comparison of Serum tumor marker levels, immunoglobulin levels and adverse effects in patients

Before treatment, no statistically significant differences existed in the levels of serum tumor markers (CEA, AFP, CA19-9, NSE and CA125) among the three groups (all P>0.05). After treatment, CEA, CA19-9, NSE, and CA125 levels decreased significantly in all three groups, while AFP levels decreased significantly only in the Immunotherapy+chemotherapy group (all P<0.05).

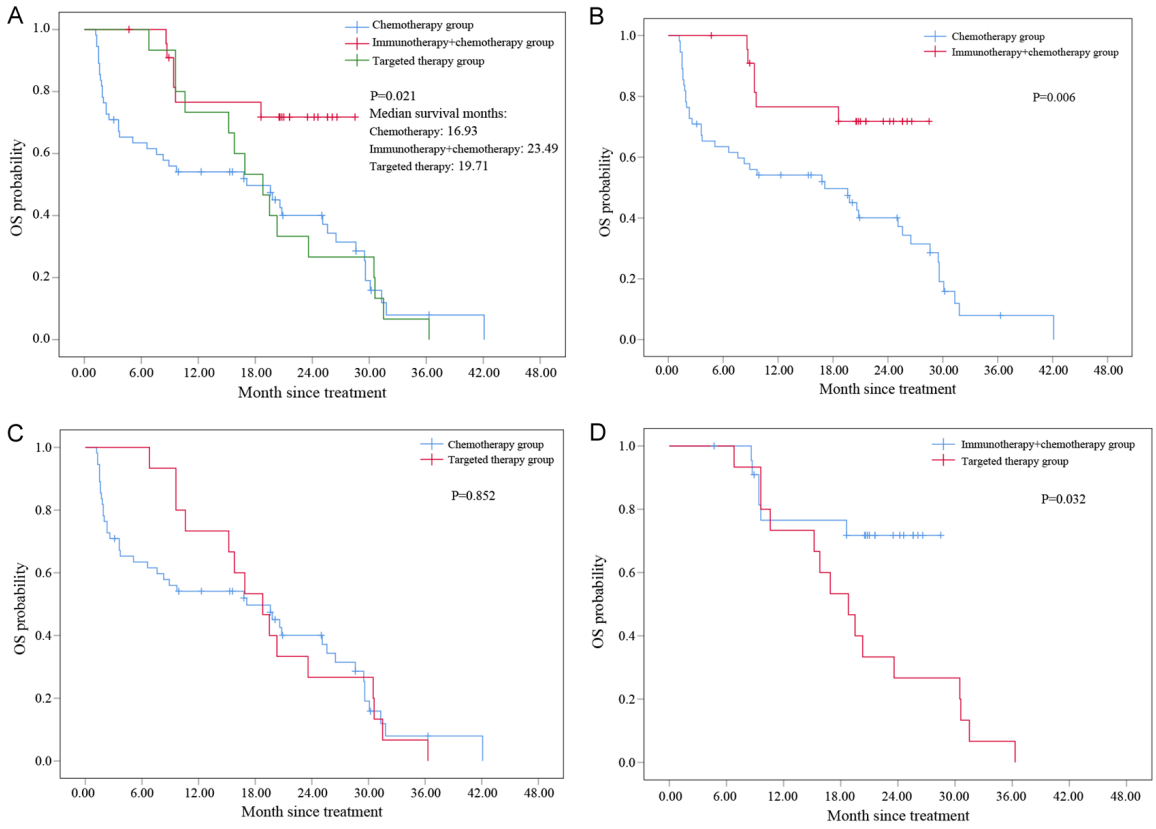

Figure 2. Kaplan-Meier overall survival curves for patients with stage IIIB/IV LCNEC receiving different treatment regimens. A: Comparison of OS between three groups (log-rank test, P=0.021). Median OS: Chemotherapy=16.93 months, Immunotherapy+chemotherapy group=23.49 months, targeted therapy group=19.71 months. B: Comparison of OS between chemotherapy and Immunotherapy+chemotherapy group (log-rank test, P=0.006). C: Comparison of OS between chemotherapy and targeted therapy group (log-rank test, P=0.852). D: Comparison of OS between Immunotherapy+chemotherapy group and targeted therapy group (log-rank test, P=0.032).

Table 2. Impact of various variables on PFS and OS

Univariate	mPFS 95% CI (mo)	*P*-value	mOS 95% CI (mo)	*P*-value
Age (≤66/>66)	1.167 (0.709-1.920)	0.544	1.496 (0.892-2.508)	0.127
Gender (Male/Female)	0.783 (0.450-1.363)	0.388	0.954 (0.549-1.659)	0.868
Smoking (Yes/No)	1.154 (0.701-1.900)	0.574	0.988 (0.599-1.632)	0.963
PS (0-1/2-3)	1.148 (0.596-2.214)	0.680	1.750 (0.901, 3.402)	0.099
Treatment regimens				0.41
Chemotherapy	-	0.000	-	0.032
Immunotherapy+chemotherapy group	0.134 (0.052-0.345)	0.000	0.314 (0.132-0.747)	0.009
Targeted therapy group	1.206 (0.656-2.218)	0.546	0.925 (0.510-1.678)	0.798

Abbreviations: PS, performance status; CI, confidence interval; mPFS, median progression free survival; mOS, overall survival.

Meanwhile, there were statistically significant differences in post-treatment CEA (P=0.001) and CA125 (P=0.028) levels among the three groups specifically, the Immunotherapy+chemotherapy group had significantly lower levels of these two markers than the chemotherapy group, but no significant difference was observed between the Immunotherapy+chemotherapy group and the targeted therapy group (P>0.05, **Table 3**). Before treatment, no statistically significant differences existed in immunoglobulin (IgA, IgG and IgM) levels am-

Table 3. Comparison of the levels of serum tumor markers in each group

		Chemotherapy (n=55)	Immunotherapy+ chemotherapy group (n=23)	Targeted therapy group (n=15)	F	*P*-value
Before treatment	CEA (μg/L)	6.29±1.35	6.30±0.90	6.34±1.45	0.009	0.991
	AFP (μg/L)	14.15±3.69	14.96±3.31	14.39±2.32	0.455	0.636
	CA19-9 (ku/L)	32.19±5.47	31.74±3.80	33.87±6.41	0.800	0.452
	NSE	18.06±2.46	19.43±3.52	18.47±2.67	1.959	0.147
	CA125 (ku/L)	30.88±8.16	30.47±5.94	29.43±6.54	0.226	0.798
After treatment	CEA (μg/L)	5.48±1.97*	3.64±1.48*,a	4.72±2.03*	7.918	0.001
	AFP (μg/L)	13.95±2.65	13.14±2.74*	14.34±2.25	1.142	0.324
	CA19-9 (ku/L)	29.23±5.43*	27.81±4.55*	27.03±5.67*	1.308	0.275
	NSE (mg/ml)	16.35±2.98*	14.90±2.45*,a	15.34±3.70*	2.149	0.123
	CA125 (ku/L)	16.75±3.61*	14.63±2.53*,a	15.43±2.86*	3.705	0.028

Notes: *P<0.05 vs before treatment in same group; aP<0.05 vs chemotherapy group.

Table 4. Comparison of the immunoglobulin levels in each group

		Chemotherapy (n=55)	Immunotherapy+chemotherapy group (n=23)	Targeted therapy group (n=15)	F	*P*-value
Before treatment	IgA	2.07±0.22	2.08±0.31	2.11±0.42	0.115	0.892
	IgG	8.58±1.12	9.06±1.02	8.38±2.09	1.510	0.227
	IgM	1.81±0.33	1.91±0.34	1.93±0.29	1.199	0.306
After treatment	IgA	1.29±0.32*	1.53±0.19*,a	1.44±0.21*	6.434	0.002
	IgG	6.68±1.18*	7.33±0.82*,a	6.87±1.01*	3.239	0.044
	IgM	1.25±0.25*	1.49±0.24*,a	1.36±0.22*	8.360	0.001

Notes: *P<0.05 vs before treatment in same group; aP<0.05 vs chemotherapy group.

ong the three groups (all P>0.05). After treatment, the levels of IgA, IgG, and IgM were significantly lower than baseline in all three groups (all P<0.05). However, the Immunotherapy+ chemotherapy group had higher IgA, IgG, and IgM levels than the chemotherapy group (all P<0.05) (**Table 4**).

No significant difference was found in the incidence of adverse events among the three groups (P>0.05; **Table 5**).

Comparison of patient QoL

Before treatment, no significant differences existed in QoL scores across all dimensions (physical, social/family well-being, emotional, and functional well-being and additional lung cancer-specific concerns) (all P>0.05). After treatment, the chemotherapy group showed a significant increase only in emotional well-being scores (P<0.05). The Immunotherapy+ chemotherapy group showed significant increases in scores across all QoL domains (all P<0.05). The targeted therapy group showed significant increases in scores for emotional well-being, functional well-being, and additional lung cancer-specific concerns (all P< 0.05). Moreover, there were significant differences in terms of the scores of physical (P=0.0003), social/family (P=0.001), emotional (P=0.009) and functional (P=0.017) well-being among the three groups. Also, the scores of physical and functional well-being were significantly higher in both the Immunotherapy+ chemotherapy group and the targeted therapy group than those in the chemotherapy group; while social/family well-being scores were higher in the Immunotherapy+chemotherapy group than that in the chemotherapy and targeted therapy group (all P<0.05) (**Table 6**).

Discussion

The prognosis of LCNEC remains poor due to the lack of optimal treatment strategies for this rare lung cancer subtype. The rarity of LCNEC poses a major obstacle to conducting prospec-

Table 5. Comparison of the occurrence of grade III-IV adverse reactions in each group

Group	Neutropenia	Thrombocytopenia	Anemia	Nausea and vomiting	Lacking in strength	Liver function damage	Renal function damage	Total incidence
Chemotherapy (n=55)	25 (45.5)	18 (32.7)	18 (32.7)	33 (60.0)	37 (67.3)	13 (23.6)	14 (25.5)	36 (65.5)
Immunotherapy+chemotherapy group (n=23)	12 (52.2)	9 (39.1)	6 (26.1)	12 (52.2)	13 (56.5)	8 (34.8)	6 (26.1)	14 (60.9)
Targeted therapy group (n=15)	8 (53.3)	5 (33.3)	5 (53.3)	9 (60.0)	9 (60.0)	6 (40.0)	6 (40.0)	10 (66.7)
X^2	0.468	0.304	0.372	0.436	0.899	2.022	1.291	0.185
P-value	0.791	0.859	0.830	0.804	0.638	0.364	0.524	0.912

Table 6. Comparison of the quality of life

		Chemotherapy (n=55)	Immunotherapy+chemotherapy group (n=23)	Targeted therapy group (n=15)	F	*P*-value
Before treatment	Physical well-being	19.76±2.49	19.70±2.58	19.43±3.22	0.092	0.912
	Social/family well-being	19.65±5.21	19.13±5.48	20.17±3.95	0.193	0.825
	Emotional well-being	11.96±2.49	12.26±2.36	12.04±1.97	0.128	0.880
	Functional well-being	15.55±5.35	17.04±3.91	15.78±5.53	0.710	0.494
	Additional lung cancer-specific concerns	25.67±4.63	24.00±4.37	25.52±4.49	1.130	0.328
After treatment	Physical well-being	19.49±2.33	21.96±3.21^{*,a}	21.39±2.02^{a}	9.064	0.0003
	Social/family well-being	20.82±3.24	23.83±3.31^{*,a}	21.57±2.29^{b}	7.515	0.001
	Emotional well-being	13.02±2.50*	15.04±2.96^{*,a}	14.13±2.56*	5.028	0.009
	Functional well-being	17.04±3.86	19.26±3.31^{*,a}	19.30±3.05^{*,a}	4.300	0.017
	Additional lung cancer-specific concerns	26.71±2.90	27.39±2.71*	26.74±4.11	0.415	0.661

Notes: *P<0.05 vs before treatment in same group; ^{a}P<0.05 vs chemotherapy group; ^{b}P<0.05 vs Immunotherapy+chemotherapy group.

tive clinical trials, rendering data on the efficacy of treatment regimens, particularly immunotherapy, elusive in large first-line or later-stage cohorts. In the present study, we aimed to compare the efficacy of different first-line treatment strategies in patients with stage IIIB/IV LCNEC.

Given the clinical pathological and biological similarities between LCNEC and small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC) [27], the chemotherapy regimens in this study were consistent with the classic protocols for these two diseases. Notably, platinum-based chemotherapy combined with pemetrexed is recommended as first-line treatment for patients with metastatic non-squamous NSCLC [30]. Biologically, SCLC shares close similarities with LCNEC [27]. We found that the efficacy of chemotherapy alone was comparable to the previous studies: the ORR and mPFS of the chemotherapy-alone group aligned with existing literature, which documents ORRs of 34.0%-46.0% and mPFS of 4.4-5.8 months [7, 31-33].

A notable finding of our study is that the mPFS in the Immunotherapy+chemotherapy group was significantly longer than that in the chemotherapy group, consistent with results from recent large-scale trials [14, 34, 35]. Similar outcomes have been observed in other studies. For example, Song et al. found that first-line pembrolizumab plus chemotherapy yielded a better prognosis than chemotherapy alone, with a median PFS of 7.0 months and median OS of 24.0 months in the combination group [36]. Additionally, As reported by Komiya et al. [37], in patients with stage IV LCNEC, immunotherapy administration (irrespective of treatment setting) resulted in better OS outcomes than non-administration, with the Immunotherapy+chemotherapy group showing higher 12-month and 18-month survival rates [37]. In our study, the immunotherapy combined with chemotherapy group exhibited superior ORR and DCR compared with the chemotherapy group. Survival curves also revealed a trend toward better survival benefit in the Immunotherapy+chemotherapy group, which may be attributed to the higher proportion of patients in this group who did not experience PD and reached the survival endpoint.

Furthermore, the survival benefit of the Immunotherapy+chemotherapy group became more pronounced with extended follow-up. Our univariate analysis demonstrated a significant difference in mPFS between the chemotherapy and Immunotherapy+chemotherapy groups, highlighting the potential of integrating immunotherapy into first-line treatment for advanced LCNEC. Chauhan et al. [38] also reported three cases of LCNEC patients who progressed on platinum-based chemotherapy but achieved durable responses (complete radiological response or disease stabilization) after switching to nivolumab. Collectively, these results provide clinical evidence that immunotherapy may be a promising first-line treatment strategy to improve survival outcomes in advanced LCNEC.

It is crucial to acknowledge the limitations of our study. First, its single-center, real-world retrospective design and small sample size may restrict result generalizability. Second, the immunotherapy plus chemotherapy group had a relatively high proportion of patients without PD, which could exaggerate the regimen's survival benefit and bias intergroup efficacy comparisons. Additionally, inherent biases and incomplete information are also unavoidable in retrospective studies. Furthermore, driver gene alterations were not detected in nearly 50% of our patients, limiting assessment of targeted therapy. Therefore, large-scale prospective studies are needed to clarify the optimal advanced LCNEC therapies. Such studies should include comprehensive genetic profiling, standardized enrollment to reduce intergroup imbalances, and extended follow-up to evaluate long-term survival.

In conclusion, our study provides preliminary evidence that chemotherapy combined with immunotherapy may be a beneficial first-line treatment strategy for patients with stage IIIB/IV LCNEC. Furthermore, EGFR-TKI targeted therapy shows encouraging results in EGFR-mutant patients. Future research should also explore the role of other novel immunotherapeutic agents, targeted therapies, and their combinations to further improve outcomes for patients with advanced LCNEC.

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Disclosure of conflict of interest

None.

Address correspondence to: Zhuoran Li, Department of Oncology, The First Affiliated Hospital of Henan Medical University, Xinxiang Key Laboratory of Diagnosis and Treatment of Thoracic Cancer (Lung and Esophagus), Weihui 453100, Henan, China. Tel: +86-0373-4404331; E-mail: ranzeal@163.com

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