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Original Article

Etoposide plus cisplatin chemotherapy improves the efficacy and safety of small cell lung cancer

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Abstract: Background: According to the statistical data of GLOBOCAN in 2020, the incidence of lung cancer ranks third worldwide. Approximately 60%-70% of newly diagnosed patients with small cell lung cancer (SCLC) has already progressed to extensive-stage SCLC (ES-SCLC). SCLC is sensitive to chemotherapy and radiotherapy, but prone to secondary drug resistance. At present, chemotherapy is the mainstay of treatment for ES-SCLC. This study is designed to evaluate the efficacy and safety of etoposide plus platinum in the treatment of SCLC. Methods: A retrospective analysis was performed on 112 patients with SCLC admitted to the China-Japan Union Hospital of Jilin University from 2016 to 2018. According to treatment methods, the patients were divided into an EL group (etoposide plus lobaplatin, n = 53) and an EP group (etoposide plus cisplatin, n = 59). The short-term efficacy (objective response rates and disease control rates) and 2-year survival rates were observed. The two groups were compared in terms of serum levels of pro-gastrin-releasing peptide (ProGRP), neuron-specific enolase (NSE), vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) before and after treatment. The incidence of adverse reactions was also compared. The quality of life (QOL) of patients was compared by measuring the Karnofsky Performance Status (KPS) scale. The risk factors affecting treatment efficacy were analyzed by multivariate Logistics analysis. Results: Patients in the EL group had similar objective response rate (ORR) and disease control rate (DCR) to those in the EP group. The 2-year survival prognosis (median survival time) between the two groups was not significantly different. After treatment, serum levels of ProGRP, NSE, VEGF and MMP-9 in both groups decreased remarkably, with no remarkable differences between the two groups. The EL group had a remarkably lower incidence of adverse reactions than the EP group. In the EP group, the KPS scores after 6 cycles of treatment were remarkably higher than those after 2 cycles of treatment. ProGRP, NSE, VEGF and MMP-9 were independent risk factors affecting the efficacy of patients with SCLC. Conclusion: With equivalent efficacy, EP regimen is safer than EL regimen in the treatment of SCLC, which suggests that etoposide plus platinum has better clinical application value for SCLC.

Keywords: Etoposide, cisplatin, lobaplatin, objective response rate, adverse reaction

Introduction

As an aggressive subtype of lung cancer, small cell lung cancer (SCLC) accounts for 15% of the total number of lung cancer [1, 2]. Characterized by rapid growth, susceptibility to distant metastasis and high degree of malignancy, SCLC is closely related to the exposure of tobacco carcinogens [3, 4]. Clinically, patients with SCLC can be divided into the ones with extensive- and limited-stage. Most of the SCLC patients are in the extensive-stage at the time of diagnosis, with poor prognoses [5]. Extensive-stage SCLC (ES-SCLC) is usually treated by platinum-based chemotherapy, but patients are generally insensitive to second-line treatment, with only a small proportion of patients achieving complete remission [6]. According to epidemiological data, although the incidence of SCLC shows a downward trend, the median survival time (MST) of patients is still as low as 7 months [7]. Therefore, it is still urgent and important to optimize the treatment of ES-SCLC so as to improve the prognosis of patients.

Etoposide, essentially a topoisomerase 2A (TOP2A) inhibitor, is usually used as a first-line chemotherapy drug for tumors [8]. Its combination with cisplatin, which is a combined

chemotherapy regimen, is also commonly used as a first-line treatment regimen for ES-SCLC [9]. However, in addition to drug resistance, cisplatin also has neurotoxicity, gastrointestinal toxicity, ototoxicity and nephrotoxicity, which hinders the exertion of therapeutic effects [10, 11]. Lobaplatin, with equivalent anti-tumor ability to cisplatin, is a third-generation platinum drug that can attenuate drug resistance and improve stability with relatively low toxicity [12, 13]. In the reports by Li [14] and others, the toxicity of lobaplatin plus etoposide (an EL regimen) is remarkably lower than that of cisplatin plus etoposide (an EP regimen) in the gastrointestinal tract. Additionally, the EL regimen has also been used to treat male patients with ES-SCLC over 65 years old, and has been shown to inhibit tumor progression and improve the patients' survival outcomes [15].

The innovation of this study lies in the comparison and evaluation of the application of EL regimen and EP regimen in ES-SCLC from the perspectives of short-term efficacy, prognosis, serum tumor markers, serum indicators, safety and quality of life (QOL), which may be beneficial to improving the management of ES-SCLC.

Materials and methods

General information

Admitted to The China-Japan Union Hospital of Jilin University from 2016 to 2018, 112 patients with SCLC were retrospectively analyzed, and divided into an EL group (etoposide plus lobaplatin, n = 53) and an EP group (etoposide plus cisplatin, n = 59) based on treatment methods. Among them, 30 males and 23 females were in the EL group, with 35 males and 24 females in the EP group. This study has been approved by the Ethics Committee of this hospital. The subjects and their guardians have been informed of this study and signed the fully informed consent form. Inclusion criteria: Patients diagnosed with SCLC by pathology and imaging; Patients with extensive neoplasms confirmed by general examination; patients aged 18-75; patients with a Performance Status (PS) score of 0-2 point(s) [16]; Patients with normal bone marrow and liver function; Patients with at least two cycles of chemotherapy and at most six cycles until disease progression or intolerable toxicity occurred; patients who could receive 2-year follow-ups; Patients with complete medical records and follow-up data. Exclusion criteria: Those with other malignant tumors; those with other types of lung cancer; those with severe visceral, systemic, metabolic or infectious diseases; those with other lung diseases; those with chemotherapy contraindications; those who were allergic to the drugs used in this study; those who cannot cooperate independently to complete this study; those with severe mental disorders. The inclusion criteria were applicable to both EL and EP groups.

Therapeutic methods

EL group: The patients were treated with etoposide plus lobaplatin. Lobaplatin (Phystandard Bio-Tech Co., Ltd., Shenzhen, China, L11943) was intravenously dripped at 50 mg/m^2 on the first day, and etoposide (Baomanbio, Shanghai, China, D1597) was given intravenously at 100 mg/m^2 on days 1-3, with 21 days as a cycle of treatment.

EP group: The patients were treated with etoposide plus cisplatin. Cisplatin (Acmec, Shanghai, China, C14330-5g) was intravenously dripped at 80 mg/m^2 on the first day, and etoposide at 100 mg/m^2 on days 1-3, with 21 days as a cycle of treatment.

Both groups of patients were given glastron antiemetics for antiemetics, and the patients were reminded to eat more light and digestible foods for gastroprotective treatment. EP group was given hydration and diuretic treatment. Specifically, 1000 mL 5% GNs + 10 mL 10% KCL was injected intravenously, and then cisplatin was added into 200 mL NS by intravenous infusion and finished within 30-40 min. After the infusion of cisplatin, 250 mL 20% mannitol was intravenously administered, and the infusion was completed in 20-30 min. In addition, a large amount of fluid should be given to achieve diuretic effect. Blood routine examination twice a week, liver and kidney function once a week. Blood routine examinations were conducted twice a week, and hepatic and renal function tests were conducted once a week.

Efficacy evaluation

Treatment efficacy was evaluated based on the Response Evaluation Criteria in Solid Tumors

Table 1. Baseline data of EL and EP groups [n (%), mean ± SD]

Factors	n	EL group (n = 53)	EP group (n = 59)	χ^2/t	P
Age (Years)				0.055	0.814
≤ 65	71	33 (62.26)	38 (64.41)		
> 65	41	20 (37.74)	21 (35.59)		
Gender				0.085	0.771
Male	65	30 (56.60)	35 (59.32)		
Female	47	23 (43.40)	24 (40.68)		
BMI				0.057	0.972
< 18.5	23	11 (20.75)	12 (20.34)		
18.5-25	52	24 (45.28)	28 (47.46)		
> 25	37	18 (33.97)	19 (32.20)		
KPS score (points)				0.275	0.600
0-1	69	34 (64.15)	35 (59.32)		
2	43	19 (35.85)	24 (40.68)		
History of smoking				0.141	0.708
Yes	78	36 (67.92)	42 (71.19)		
No	34	17 (32.08)	17 (28.81)		
First-line treatment efficacy				0.165	0.869
CR	24	11 (20.75)	13 (22.03)		
PR + SD	88	42 (79.25)	46 (77.97)		
First-line treatment cycle (n)				0.025	0.875
4	41	19 (35.85)	22 (37.29)		
6	71	34 (64.15)	37 (62.71)		
Number of metastatic lesions (n)				0.943	0.624
1	15	8 (15.09)	7 (11.86)		
2	41	17 (32.08)	24 (40.68)		
≥ 3	56	28 (52.83)	28 (47.46)		
Metastatic sites				0.407	0.524
Intrapulmonary	35	15 (28.30)	20 (33.90)		
Extrapulmonary	77	38 (71.70)	39 (66.10)		

Table 2. Clinical efficacy in both groups [n (%)]

Groups	n	CR	PR	SD	PD	ORR	DCR
EL group	53	9 (16.98)	20 (37.74)	10 (18.87)	14 (26.42)	29 (54.72)	39 (73.58)
EP group	59	6 (10.17)	21 (35.59)	7 (11.86)	25 (42.37)	27 (45.76)	34 (57.63)
χ^2 value	-	-	-	-	-	0.895	3.133
P value	-	-	-	-	-	0.344	0.077

(RECIST), the World Health Organization criteria [17]. Complete response (CR) signified that the lesion disappeared completely and the duration was ≥ 4 weeks; partial response (PR) indicated that the lesion diameter was reduced by ≥ 30% and the duration was ≥ 4 weeks; progressive disease (PD) signified new lesions appeared and the lesion diameter increased by ≥ 20%; stable disease (SD) signified that the lesion diameter decreased or increased to between PR and PD.

The objective response rate (ORR) was the percentage of the sum of CR and PR in the total number of cases.

The disease control rate (DCR) was the percentage of the sum of CR, PR and SD in the total number of cases.

Outcome measures

Tumor markers of patients in both groups before and after treatment were compared by

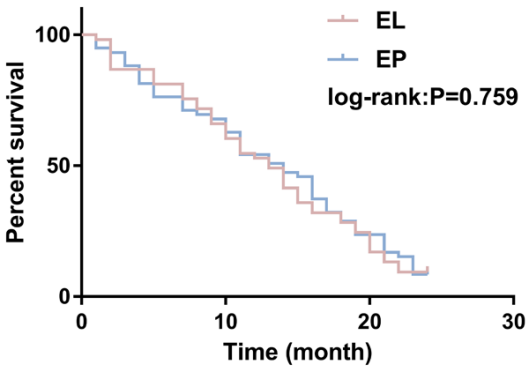

Figure 1. Comparison of 2-year survival rates. There was no significant difference in the 2-year OS between EL and EP groups (9.43% VS 8.47%).

enzyme-linked immunosorbent assays (ELISAs) [18]. The fasting elbow venous blood of patients in both groups was collected at 8 am. Serum pro-gastrin-releasing peptide (ProGRP) and neuron-specific enolase (NSE) in both groups were detected with human ProGRP ELISA kits and human NSE ELISA kits respectively (Wuhan Yipu Biotechnology Co., Ltd., Wuhan, China, CK-E10367, CK-E11106).

ELISAs were also performed to compare the serum vascular endothelial growth factor (VEGF) and the matrix metalloproteinase-9 (MMP-9) of patients in both groups before and after treatment. VEGF and MMP-9 levels were detected using human VEGF ELISA kits and human MMP-9 ELISA kits respectively (Fuyu Biotechnology Co., Ltd., Shanghai, China, FY-04187H2, FY-04296H1).

The incidence of adverse reactions, which mainly included leukopenia, neutropenia, anemia, stomatitis, alopecia and hepatic dysfunction, was compared between the two groups.

The quality of life (QOL) was compared by the Karnofsky Performance Status (KPS) scores [19] between the two groups. The score, ranging from 0 to 100 point (s), was directly proportional to the QOL.

Follow-ups

Follow-ups were performed once every three months for two years, mainly through telephone interviews and inquiring pathological data. Overall survival (OS) was from the beginning of the treatment to the death of the patients or the end of the 2-year follow-up, whichever came first.

Statistical analysis

GraphPad Prism 6 (GraphPad Software, San Diego, USA) was used to analyze data and plot figures. Enumeration data were expressed by the number of cases/percentages (n/%), while measurement data were expressed as mean ± SEM. Enumeration data were compared between groups by a chi-square test; When the theoretical frequency in the chi-square test was less than 5, the comparison was conducted by a chi-square test with correction for continuity. Measurement data were compared between groups by an independent samples t test and within groups before and after treatment by a paired t test. Logistics multivariate analysis was conducted to analyze the risk factors affecting the efficacy of patients. When $P < 0.05$, the difference is statistically significant.

Results

Baseline data

Patients in the two groups were not remarkably different in age, gender, body mass index (BMI), KPS score, history of smoking, first-line treatment efficacy, first-line treatment cycle and the number of metastatic lesions ($P > 0.05$) (**Table 1**).

Comparison of short-term efficacy

The short-term efficacy was compared between the two groups. The number of patients with CR, PR, SD and PD in the EL group was 5, 16, 8 and 24, respectively, while that in the EP group was 6, 21, 10 and 22, respectively. The ORR and the DCR in the EL group were 54.72% and 73.58%, respectively, while those in the EP group were 45.76% and 57.63%, respectively. The two groups were not remarkably different in the ORR and the DCR ($P > 0.05$) (**Table 2**).

Comparison of 2-year survival rates

The patients were followed up for 2 years. All patients successfully completed the follow-ups with a 2-year OS of 8.93%. The 2-year OS rates in the EL and EP groups were 9.43% and

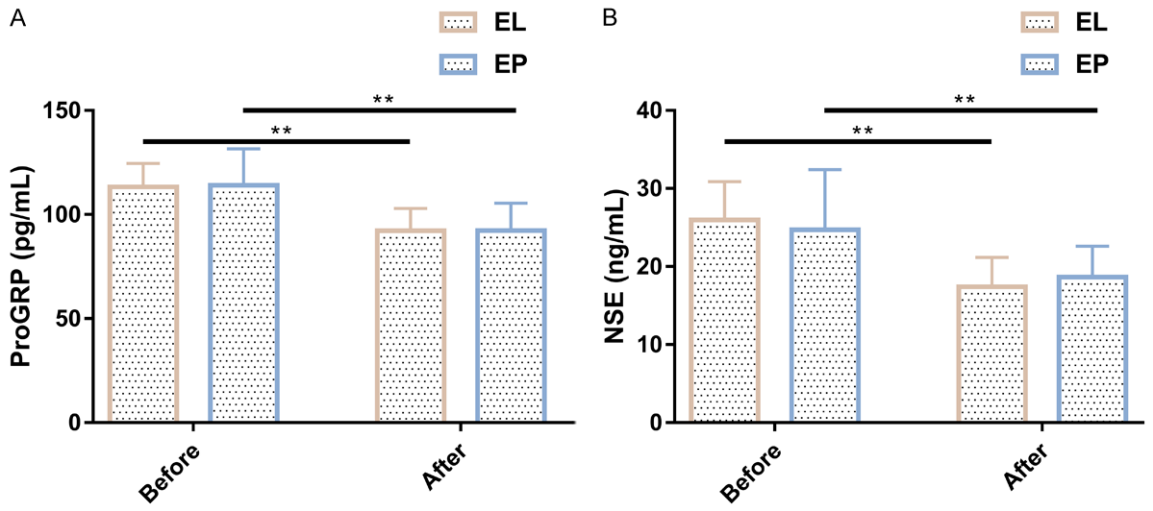

Figure 2. Tumor markers in both groups. A. The ProGRP decreased significantly in both groups after treatment, but with no significant difference between the two groups. B. The NSE reduced significantly in both groups after treatment, but with no significant difference between the two groups. Note: ** indicates $P < 0.01$ *vs* before treatment.

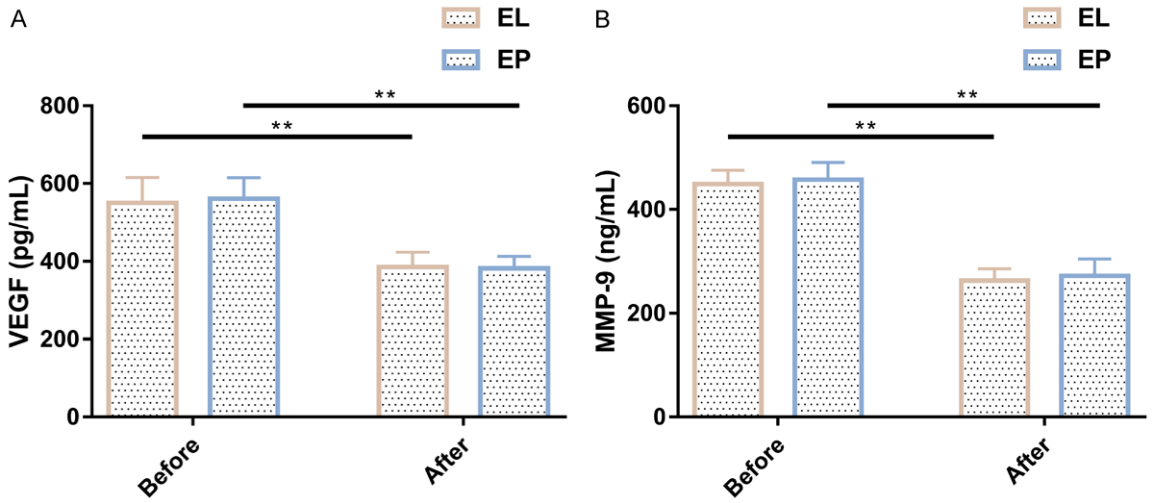

Figure 3. VEGF and MMP-9 in both groups. A. The VEGF decreased significantly in both groups after treatment, but with no significant difference between the two groups. B. The MMP-9 reduced significantly in both groups after treatment, but with no significant difference between the two groups. Note: ** indicates $P < 0.01$ *vs* before treatment.

Table 3. Incidence of adverse reactions in both groups [n (%)]

Categories	EL group (n = 53)	EP group (n = 59)	χ^2 value	*P* value
Leukopenia	3 (5.66)	9 (15.25)	-	-
Neutropenia	4 (7.55)	8 (13.56)	-	-
Anemia	2 (3.77)	7 (11.86)	-	-
Stomatitis	0 (0.00)	4 (6.78)	-	-
Alopecia	0 (0.00)	2 (3.39)	-	-
Hepatic dysfunction	3 (5.66)	6 (10.17)	-	-
Total	12 (22.64)	36 (61.02)	16.789	< 0.001

8.47%, respectively, and the MST was 13 months and 11 months, respectively, with no remarkable differences between the two groups ($P > 0.05$) (**Figure 1**).

Tumor markers in the two groups

Tumor markers (ProGRP and NSE) were detected in both groups. The data showed that before treat-

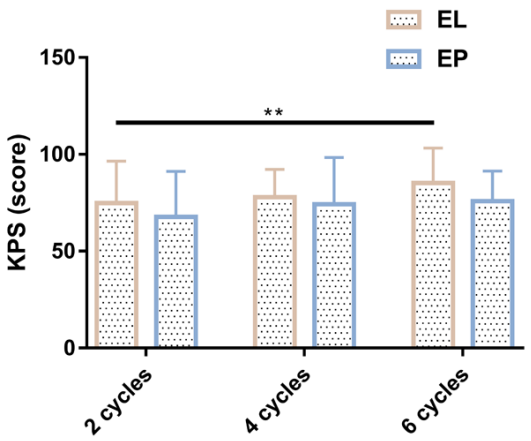

Figure 4. QOL in both groups. In the EL group, the KPS score at 6 cycles of treatment was significantly higher than that at 2 cycles of treatment. Note: ** indicates P < 0.01 *vs* before treatment.

Table 4. Assignment for multivariate Logistic regression analysis

Factors	Variables	Assignment
ProGRP (pg/mL)	X1	A continuous variable
NSE (ng/mL)	X2	A continuous variable
VEGF (pg/mL)	X3	A continuous variable
MMP-9 (ng/mL)	X4	A continuous variable

ment, ProGRP and NSE were not remarkably different between the two groups (P > 0.05); The two tumor markers remarkably decreased in both groups after treatment (P < 0.05), but with no significant difference between the two groups (P > 0.05) (**Figure 2**).

VEGF and MMP-9 in the two groups

Serum indices such as VEGF and MMP-9 were measured to analyze the effects of the two treatment methods on the angiogenesis and inflammation of patients. The data showed that before treatment, VEGF and MMP-9 were not remarkably different between the two groups (P > 0.05); The two inflammatory indices reduced significantly in both groups after treatment (P < 0.05), but without significant difference between the two groups (P > 0.05) (**Figure 3**).

Comparison of incidence of adverse reactions

The incidence of adverse reactions was recorded in both groups. The number of cases of leukopenia, neutropenia, anemia, stomatitis, alopecia and hepatic dysfunction in the EL group was 3, 4, 2, 0, 0 and 3, respectively, while that in the EP group was 9, 8, 7, 4, 2 and 6, respectively. The EL group had a remarkably lower total incidence than the EP group (22.64% VS 61.02%; P < 0.05) (**Table 3**).

QOL in the two groups

The QOL in both groups was evaluated by the KPS scale. The results showed that the KPS scores after 2, 4 and 6 cycles of treatment were not remarkably different between the two groups (P > 0.05). In the EP group, the scores after 2, 4 and 6 cycles of treatment were not remarkably different (P > 0.05), while in the EL group, the scores after 6 cycles of treatment were remarkably higher than those after 2 cycles of treatment (P < 0.05) (**Figure 4**).

Analysis of risk factors affecting the efficacy of patients with SCLC

For analysis, factors with differences (ProGRP, NSE, VEGF and MMP-9) were included and assigned as dependent variables. With whether it affected the efficacy of patients with SCLC as the dependent variable, the multivariate analysis was performed with a Logistic regression model. The results showed that ProGRP (P = 0.003), NSE (P = 0.006), VEGF (P = 0.035) and MMP-9 (P = 0.046) were independent risk factors affecting the efficacy (**Tables 4**, **5**).

Discussion

As a fatal neuroendocrine tumor, SCLC is one of the leading causes of cancer-related death in men and women worldwide [20, 21]. Although the early treatment of SCLC is effective, patients will eventually die due to recurrence caused by drug resistance, especially for those receiving EP regimen [22]. Therefore, it is essential to further explore treatment methods superior to the EP regimen for improving the prognosis of patients with SCLC.

In this study, the ORR and DCR in the EL group were 54.72% and 73.58%, respectively, while those in the EP group were 45.76% and 57.63%, respectively. The two indicators were not remarkably different between the two groups. This suggests that the short-term efficacy of the two regimens is almost equivalent. In terms of prognosis, the 2-year OS was not remarkably different between the two groups; The OS in the EL and EP groups was 9.43%

Table 5. Multivariate analysis of factors affecting efficacy on patients with SCLC

Factor	β	S.E	Wald	P	OR	95% CI
ProGRP (pg/mL)	2.387	0.784	8.725	0.003	10.057	2.159-46.572
NSE (ng/mL)	1.450	0.524	7.733	0.006	4.256	1.548-11.820
VEGF (pg/mL)	1.301	0.622	4.348	0.035	3.652	1.084-12.339
MMP-9 (ng/mL)	1.375	0.689	4.054	0.046	3.957	1.054-15.122

and 8.47%, respectively, and the MST was 13 months and 11 months, respectively, which are similar to the findings of Gu [23] and other researchers. This demonstrates that the improvement effect of the EL regimen on the patients' prognoses is almost equivalent to that of the EP regimen. The effects of the two regimens on serum tumor markers, angiogenesis and inflammation were also evaluated. Among them, ProGRP is stably present in plasma, and can be used as an effective biological indicator of SCLC, reflecting the treatment of patients [24]. NSE, a diagnostic index of early SCLC, is related to the clinical progression of SCLC [25]. Both VEGF and MMP-9 mediate the invasive phenotypic modulation of SCLC [26]. In our study, serum levels of ProGRP, NSE, VEGF and MMP-9 in both groups decreased remarkably after treatment, but without significant difference between the two groups. As for safety, the EL group had remarkably lower total incidence of adverse reactions (leukopenia, neutropenia, anemia, stomatitis, alopecia and hepatic dysfunction) than the EP group. Zhou [27] and others reported that leukopenia and neutropenia are the most common adverse reactions in patients with ES-SCLC receiving EL regimen, which is consistent with the results of this study. Then, the QOL of the patients in both groups was evaluated. In the EL group, the KPS scores after 6 cycles of treatment were remarkably higher than those after 2 cycles of treatment. In the EP group, the scores after 2, 4 and 6 cycles of treatment were not remarkably different, with no remarkable differences in the scores between two groups in each period. Taken gogether, we may conclude that although EL and EP were similar in short-term efficacy, 2-year prognosis, serum tumor, angiogenesis, and inflammation, the EL program is significantly better than the EP in terms of safety and quality of life improvement. Therefore, in the treatment strategy for patients with ES-SCLC, it is recommended that clinicians prioritize EL over EP as a treatment option. Finally, the risk factors affecting the efficacy of patients with SCLC were analyzed. The data showed that ProGRP, NSE, VEGF and MMP-9 were independent risk factors affecting the efficacy of patients with SCLC.

The novelty of this study lies in the comparison of the EL and EP regimens from the aspects of efficacy, prognosis, serum tumors, safety and QOL, demonstrating that the EL regimen has a better clinical application value for ES-SCLC. However, this study still needs to be improved. First, the clinical samples can be increased to improve the accuracy of tests. Second, the fundamental research of the EL regimen can be supplemented to explore its regulatory mechanisms. Third, we can also use drug dose and duration of administration as variables for extensive SCLC treatment, respectively, to explore the best drug dose and duration of administration. Last but not the least, we can supplement the *in vivo* drug concentration detection of patients, and specify personalized medication schemes according to patients' BMI, ZPS score and other conditions to explore whether the treatment effect can be optimized.

In summary, the efficacy of the EP regimen in the treatment of ES-SCLC is equivalent to that of the EL regimen, but the latter has higher safety and better clinical application value.

Disclosure of conflict of interest

None.

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