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ORIGINAL ARTICLE

A comparative study on etoposide combined with lobaplatin or cisplatin in the first-line treatment of extensive-stage small cell lung cancer

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Summary

Purpose: *To compare the efficacy and safety of etoposide combined with lobaplatin or cisplatin in the first-line treatment of extensive-stage small cell lung cancer (SCLC).*

Methods: *A total of 98 extensive-stage SCLC patients treated at the Oncology Department from March 2015 to March 2017 were enrolled and divided into etoposide + lobaplatin group (EL group, n=49) and etoposide + cisplatin group (EP group, n=49) using a random number table. The clinical data of all patients were collected, and the short-term effective rate, changes in the levels of serum tumor markers carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1) and neurone specific enolase (NSE) before and after chemotherapy and adverse reactions were compared between the two groups. Moreover, the patients were followed up, and the overall survival (OS) and progression-free survival (PFS) were recorded.*

Results: *In EL group and EP group, the level of serum NSE significantly declined after treatment compared with that before treatment, but the levels of serum CEA and CYFRA21-1 were not significantly decreased after chemotherapy compared with those before chemotherapy. The incidence rate of leukopenia, erythropenia and thrombocytopenia was 71.4%, 44.9% and 40.8%, respectively, in EL group, and 85.7%, 30.6% and 24.5%, respectively, in EP group, and the degree I-II decline was more common in both groups. The proportion of gastrointestinal reactions was 14.3% and 59.2%, respectively, in EL group and EP group, with significant difference between the two groups. During follow-up, the 1-year OS was 59.2% (29/49) and 51.9% (25/49), respectively, and the 2-year OS was 26.5% (13/49) and 20.4% (10/49), respectively, in EL group and EP group. The survival curves of were plotted using the Kaplan-Meier method and log-rank test showed no statistically significant differences in the OS and PFS between the two groups.*

Conclusions: *The short-term efficacy of EL and EP regimens is equivalent in the first-line treatment of extensive-stage SCLC, both OS and PFS are similar, and the adverse reactions can be tolerated. The EL regimen produced mild gastrointestinal reactions, and is worthy of clinical popularization.*

Key words: *lobaplatin, cisplatin, etoposide, small cell lung cancer, extensive stage, efficacy*

Introduction

Lung cancer is the most common malignant tumor in the world, in which small cell lung cancer (SCLC) accounts for approximately 13%. The clinical characteristics of SCLC are poor cell differentiation, rapid proliferation, high grade of malignancy, early and extensive metastasis, and the extensive-stage SCLC accounts for about 70% of the total. Systemic chemotherapy is the dominant treatment method, which is characterized by excellent short-term efficacy, high recurrence rate and low

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cure rate. The disease relapses in more than 90% of patients after treatment, and the 5-year overall survival rate is only 1-3%, showing a very poor prognosis [1,2]. Cisplatin combined with etoposide is the most commonly used first-line chemotherapy regimen for extensive-stage SCLC in the clinic [3,4]. Due to the gastrointestinal reactions, myelosuppression and severe renal toxicity of cisplatin, the chemotherapy tolerance is rather poor, there is drug resistance or short-term recurrence after chemotherapy, and the long-term overall survival rate is low [5,6]. Therefore, exploring new combined chemotherapy regimens has become a research hotspot in recent years. Lobaplatin is a third-generation platinum antitumor drug, whose anticancer spectrum is similar to that of cisplatin, and it has equivalent or superior efficacy to the first-generation cisplatin (CDDP) and the second-generation carboplatin (CBP). Moreover, it has no cross resistance with other platinum compounds and no obvious nephrotoxicity, ototoxicity and neurotoxicity, while the toxic reactions are mild, so it has been approved as a new type of therapeutic drug for SCLC [7,8].

In the present study, 98 extensive-stage SCLC patients treated at the Oncology Department from March 2015 to March 2017 were retrospectively analyzed, the short-term efficacy, long-term efficacy and adverse reactions were observed in the treatment of extensive-stage SCLC with etoposide+lobaplatin (EL regimen) and etoposide+cisplatin regimen (EP regimen), and the effectiveness and safety of the two regimens were evaluated, so as to provide a theoretical basis for selecting the chemotherapy regimens for extensive-stage SCLC.

Methods

Study objectives

A total of 98 extensive-stage SCLC patients treated at the Oncology Department of our hospital from March 2015 to March 2017 were selected, and were initially diagnosed via biopsy and/or cytology, with an expected survival time >3 months. Extensive-stage SCLC (Veterans Administration Lung Study Group staging) was confirmed through systemic evaluation (blood and urine routine tests, electrocardiogram, hepatic and renal function electrolytes, coagulation, chest and head CT, bone scan imaging, abdominal B-ultrasound or whole body PET-CT). There was at least one measurable lesion, and the Karnofsky performance status (KPS) score was ≥60 points. Exclusion criteria: patients with other severe systemic somatic diseases, immune metabolic diseases, failure of vital organs, severe fluid and electrolyte disturbance, oropharyngeal herpes, fungal infection, bleeding tendency, severe granulocytopenia or thrombocytopenia. This study was approved by the Ethics Committee of our hospital. All patients enrolled adhered to the *Declaration of Helsinki*, they were informed and signed the informed consent.

These 98 patients were consecutively enrolled in the order of diagnosis, and divided into EL group and EP group using a random number table. In EL group, there were 49 cases, including 37 males and 12 females aged 37-77 years (mean 58.5±10.8). In EP group, there were 49 cases, including 31 males and 18 females aged 39-79 years (mean 60.7±11.1). There were no significant differences in the general characteristics, such as age, gender, KPS score and systemic metastasis, between the two groups (p>0.05), which were comparable (Table 1).

Therapeutic regimens

EL regimen: Intravenous infusion of etoposide (VP-16, Jiangsu Hengrui Medicine Co., Ltd., Lianyungang,

Table 1. Baseline characteristics of the studied patients

Parameters	*EL group (n=49) n (%)*	*EP group (n=49) n (%)*	*p value*
Age (years), mean±SD	58.5±10.8	60.7±11.1	0.323
Gender			
Male	37 (75.5)	31 (63.3)	0.273
Female	12 (24.5)	18 (36.3)	
KPS score			0.544
80-90	28 (57.1)	24 (49.0)	
60-70	21 (42.9)	25 (51.0)	
Metastasis			
Lymph node	19 (38.8)	22 (44.9)	0.682
Adrenal gland	10 (20.4)	14 (28.6)	0.482
Liver	5 (10.2)	8 (16.3)	0.553
Brain	9 (18.4)	4 (8.2)	0.233
Bone	3 (6.1)	6 (12.2)	0.487
Intrapulmonary	7 (14.3)	3 (6.1)	0.317

KPS: Karnofsky performance status, EL: etoposide+iobaplatin, EP: etoposide+cisplatin

China) (100 mg/m^2) on d 1-3, and intravenous infusion of lobaplatin (Hainan Changan International Pharmaceutical Co., Ltd., Haikou, China) (30 mg/m^2) on d 1. EP regimen: Intravenous infusion of etoposide (VP-16) (100 mg/m^2) on d 1-3, and intravenous infusion of cisplatin (Qilu Pharmaceutical Co., Ltd., Jinan, China) (80 mg/m^2) on d 1. The chemotherapy was administered for 21 d as a cycle (6 cycles at most) till disease progression or intolerable toxicity or request of patients for termination. All patients were routinely administered tropisetron, omeprazole and metoclopramide to prevent gastrointestinal reactions. When granulocytopenia occurred during chemotherapy, the patients were treated with recombinant human granulocyte colony stimulating factor (G-CSF). Rehydration therapy was also performed via intravenous infusion of amino acids, glucose and normal saline. The patients with infection were treated with antibiotics. Blood should be transfused if the hemoglobin level was below 60 g/L.

Observation indexes

Short-term efficacy: Fasting blood samples were collected from all patients in the morning, routine blood examinations were performed twice every week and the hepatic and renal function electrolyte examinations were performed once every week. Before chemotherapy and after continuous chemotherapy for 2 or more cycles, the serum tumor markers were examined through electrochemiluminescence, the clinical responses were observed, and the chest CT was performed to evaluate the changes in SCLC lesions. The short-term efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors 1.0 (RECIST 1.0): Complete response (CR): The tumor disappears for more than 1 month; partial response (PR): The product of 2 maximum vertical diameters of tumor is reduced by >50% for more than 1 month; stable disease (SD): The product of 2 maximum vertical diameters of tumor is reduced by <50% or increased by <25% for more than 1 month; and progressive disease (PD): The product of 2 maximum vertical diameters of tumor is increased by >25% or new lesion(s) appeared. The overall response rate (ORR) refers to the proportion of patients whose tumor volume shrinks to a predetermined degree for the minimum time (ORR=PR+CR). The disease control rate (DCR) is the percentage of CR+PR+SD cases in the total.

Adverse reactions: The adverse reactions were classified into grade 0-IV according to the WHO grading criteria for acute and subacute adverse reactions of antitumor drugs. The changes in serum tumor markers carcinoembryonic antigen (CEA, normal reference value: 0-3.4 ng/mL), cytokeratin 19 fragment (CYFRA21-1, normal reference value: 0-3.3 ng/mL) and neurone specific enolase (NSE, normal reference value: 0-15.2 ng/mL) before and after chemotherapy were assessed.

Survival: All patients were followed up and the OS and PFS were recorded. Those lost to follow-up were censored from the date of loss. OS refers to the duration from the first cycle of chemotherapy to the death of any cause or last follow-up. PFS refers to the duration from the first cycle of chemotherapy to the progression of disease or last follow-up.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation, and t-test was performed for the comparison between two groups. Enumeration data were expressed as rates (%), and x^2 test was performed for comparison between two groups. Kaplan-Meier curves were plotted for survival analysis, and the log-rank test was used to assess differences between groups. $P<0.05$ suggested statistically significant differences.

Results

Comparison of short-term efficacy

The efficacy of all patients was evaluated after 2-6 cycles of chemotherapy. The patients received chemotherapy for 4.34 cycles on average in EL group and 4.51 cycles on average in EP group. In EL group there were 2 cases (4.1%) with CR, 29 cases (59.2%) with PR, 11 cases (22.4%) with SD and 7 cases (14.3%) with PD, and the ORR and DCR were 63.3% (31 cases) and 85.7% (42 cases), respectively. In EP group, there was 1 case (2.0%) with CR, 26 cases (53.1%) with PR, 13 cases (26.5%) with SD and 9 cases (18.4%) with PD, and the ORR and DCR were 55.1% (27 cases) and 81.6% (40 cases),

Table 2. Short-term clinical effective rates of the two studied groups

	EL group n (%)	*EP group n (%)*	*p value*
CR	2 (4.1)	1 (2.0)	
PR	29 (59.2)	26 (53.1)	
SD	11 (22.4)	13 (26.5)	
PD	7 (14.3)	9 (18.4)	
ORR	31 (63.3)	27 (55.1)	0.538
DCR	42 (85.7)	40 (81.6)	0.785

EL: etoposide+iobaplatin, EP: etoposide+cisplatin, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ORR: objective response rate, DCR: disease control rate

respectively. There were no statistically significant differences in ORR and DCR between the two groups (p=0.538, p=0.785) (Table 2).

Comparisons of serum tumor markers levels before and after treatment

The mean level of serum CEA was 3.81±1.13 and 3.98±1.30 ng/mL before treatment in both groups, and the difference was not statistically significant (p=0.491). The mean level of serum CEA declined to 3.62±1.04 and 3.74±1.18 ng/mL after treatment in both groups, without statistically significant difference (p=0.595). The mean level of serum CYFRA21-1 was 3.91±1.07 and 3.55±1.33 ng/mL, before treatment in both groups, without statistically significant difference (p=0.143). The mean level of serum CYFRA21-1 declined to 3.81±0.93 and 3.44±1.02 ng/mL, respectively, after treatment in both groups, and there was no statistically significant difference (p=0.064). Besides, the mean serum level of NSE was 66.71±12.77 and 62.58±14.27 ng/mL, respectively, before treatment in both groups, showing no statistically significant difference (p=0.134), while it declined to 16.91±5.63 and 15.84±5.03 ng/mL, respectively, after treatment in both groups, also showing no statistically significant difference (p=0.324) (Table 3).

Comparisons of adverse reactions

The adverse reactions could be evaluated in all patients, and there were no chemotherapy-related deaths. The main side reactions were myelosuppression and gastrointestinal reactions (mainly nausea and vomiting). The reactions could be relieved in most patients after symptomatic treatment, reduction chemotherapy doses or delayed chemotherapy administration. Chemotherapy was intolerable and terminated in 1 case (2.0%) in EL group and in 1 case (2.0%) in EP group (p=0.745). Other side reactions including liver function impairment and alopecia were tolerable and could be relieved after symptomatic treatment, without

Table 3. Comparison of serum biomarkers level of lung cancer before and after chemotherapy of patients in the two studied groups (mean±SD)

	EL group	*EP group*	*p value*
Serum CEA level (ng/mL)			
Pretreatment	3.81±1.13	3.98±1.30	0.491
Posttreatment	3.62±1.04	3.74±1.18	0.595
Serum CYFRA21-1 level (ng/mL)			
Pretreatment	3.91±1.07	3.55±1.33	0.143
Posttreatment	3.81±0.93	3.44±1.02	0.064
Serum NSE level (ng/mL)			
Pretreatment	66.71±12.77	62.58±14.27	0.134
Posttreatment	16.91±5.63	15.84±5.03	0.324

KPS: Karnofsky performance status, EL: etoposide+iobaplatin, EP: etoposide+cisplatin, CEA: carcinoembryonic antigen, CYFRA: cytokeratin fragment, NSE: neurone specific enolase

Table 4. Comparison of adverse reactions of patients in the two studied groups

Parameters	*EL group n (%)*	*EP group n (%)*	*p value*
Alopecia	5 (10.2)	3 (6.1)	0.715
Anemia	1 (2.0)	3 (6.1)	0.617
Leukopenia	35 (71.4)	42 (85.7)	0.139
Thrombocytopenia	20 (40.8)	12 (24.5)	0.131
Anemia	22 (44.9)	15 (30.6)	0.211
Nausea, vomiting	7 (14.3)	29 (59.2)	0.001
Liver dysfunction	10 (20.4)	13 (26.5)	0.634
Renal dysfunction	6 (12.2)	4(8.2)	0.740
Ototoxicity	0 (0)	0 (0)	1.000
Peripheral neurotoxicity	0 (0)	0 (0)	1.000

EL: etoposide+iobaplatin, EP: etoposide+cisplatin

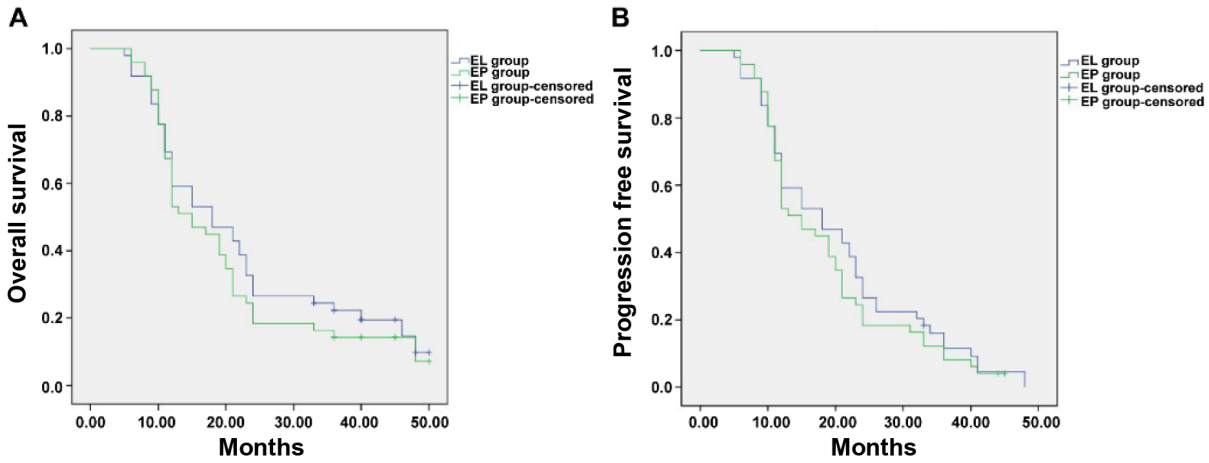

Figure 1. Kaplan-Meier survival curve of patients in EL group and EP group. **A:** The difference between overall survival rate of patients in EL group and EP group had no statistical significance (p=0.387). **B:** The difference between progression-free survival rate of patients in EL group and EP group had no statistical significance (p=0.446).

influence on chemotherapy. In terms of myelosuppression, the incidence rate of leukopenia, erythropenia and thrombocytopenia was 71.4%, 44.9% and 40.8%, respectively, in EL group, and 85.7%, 30.6% and 24.5%, respectively, in EP group, and the grade I-II decline was more common in both groups. The proportion of gastrointestinal reactions was 14.3% and 59.2%, respectively, in EL group and EP group with a significant difference between the two groups (p<0.001), and the grade I-II reactions accounted for the proportion of more. The specific adverse reactions are shown in Table 4.

Survival

All the 98 patients were followed up for 5-50 months (mean 28.9±8.6) till March 2019. During the follow-up period, the 1-year OS was 59.2% (29/49) and 51.9% (25/49), respectively, and the 2-year OS was 26.5% (13/49) and 20.4% (10/49), respectively, in EL group and EP group (p=0.034). Besides, the median PFS was 11.2 months and 9.1 months, respectively, and the median OS was 14.5 months and 13.3 months, respectively, in EL group and EP group (p=0.446). At the end of the follow-up period, 8 cases survived in EL group, including 1 case of PFS, and 6 cases survived in EP group, including 2 cases of PFS. The survival curves of patients were plotted using the Kaplan-Meier method (Figure 1). According to the log-rank test, there were no statistically significant differences in the OS and PFS between the two groups (p=0.387, p=0.446).

Discussion

SCLC is characterized by strong invasiveness capacity and short survival time, and extensive-stage SCLC accounts for 70% in the total. In extensive-stage SCLC patients, the effective rate of chemotherapy is 60-79%, PFS is 7-10 months, and the 5-year OS is 2%. Chemotherapy is an important effective treatment means for extensive-stage SCLC [10,11]. SCLC is sensitive to chemotherapeutic drugs, and the effective rate of first-line chemotherapy reaches 40-90%. However, SCLC often relapses quickly after chemotherapy, and the long-term survival rate is low. The objective of clinical treatment is to delay the progression or recurrence, prolong the survival time and improve the quality of life [12]. Cisplatin combined with etoposide is the first-line chemotherapy regimen for SCLC. It is pointed out in the NCCN guidelines for SCLC diagnosis and treatment (2010) that the chemotherapy using cisplatin combined with etoposide for 4-6 cycles is the standard regimen [13]. However, drug resistance occurs easily in cisplatin, and its mechanism involves many factors. Some studies have found that cisplatin can induce drug resistance through up-regulating the expressions of Snail protein and DNMT3a, leading to treatment failure [14]. Some patients cannot tolerate the severe myelosuppression and gastrointestinal reactions during chemotherapy, reducing the chemotherapy compliance [15]. In recent years, exploring new anti-tumor drugs and combined chemotherapy regimens has become an important way to improve the efficacy in SCLC.

In 2005, lobaplatin was approved for marketing by China's Food and Drug Agency for the treatment of advanced breast cancer, SCLC and chronic myeloid leukemia [16]. Lobaplatin has similar anticancer activity to cisplatin, and these drugs have no cross resistance, which form the intra-chain cross-linking to hinder the DNA replication and tran-

scription, selectively inhibit DNA synthesis in tumor cells, lead to inactivation of DNA template and interfere in the tumor cell cycle [17]. Lobaplatin is eliminated by the kidney within 48 h in the human body without influencing the liver, and it has good stability, broad anti-tumor spectrum, strong activity, high water solubility, and mild nephrotoxicity, gastrointestinal reactions and myelosuppression. The platelets usually decline at 2 weeks after drug administration and can be restored within 2 weeks [18]. Studies have demonstrated that lobaplatin combined with etoposide can achieve clinical efficacy comparable to that of cisplatin combined with etoposide, but the gastrointestinal reactions are severe in cisplatin, and thrombocytopenia is obvious in lobaplatin [19,20]. In the present study, it was found that there were no statistically significant differences in ORR and DCR between EL group and EP group (p=0.538, p=0.785). In terms of serum tumor markers, the level of NSE significantly declined after treatment compared with that before treatment in both groups, but the levels of CEA and CYFRA21-1 had no significant changes before and after treatment. Moreover, the follow-up results revealed that there were no statistically significant differences in the OS and PFS between the two groups (p=0.387, p=0.446), basically consistent with the findings of previous studies.

According to previous studies, the gastrointestinal reactions are milder in EL regimen than in EP regimen, and the difference is statistically significant. EL regimen is roughly similar to EP regimen in the incidence of leukopenia, anemia and thrombocytopenia, and the differences are not statistically significant. In the present study, the main toxic reaction in EL regimen was myelosuppression, especially thrombocytopenia, which is consistent with the results reported by other researchers in China. The incidence rate of leukopenia, erythropenia and thrombocytopenia was 71.4%, 44.9% and 40.8%, respectively, in EL group, and the number of cases of thrombocytopenia was larger than in EP group, but there was no statistically significant difference, possibly because of the small sample size. The incidence rate of nausea/vomiting was obviously lower in EL group than in EP group (14.3% *vs.* 59.2%, p<0.001), and other adverse reactions were mild. There are reports that the incidence rate of thrombocytopenia caused by lobaplatin is related to the creatinine clearance rate [21]: The higher the creatinine clearance rate, the milder the thrombocytopenia. When the creatinine clearance rate was above 80 mL/min, grade III-IV thrombocytopenia did not occur in 25 patients. A study by Welink et al [22] also showed that the effect of lobaplatin on thrombocytopenia is linearly associated with the area under the curve (AUC) of lobaplatin and creatinine clearance rate, and the dose adjustment can effectively prevent thrombocytopenia, demonstrating that the dosage of lobaplatin can be calculated based on the AUC and creatinine clearance rate, thereby controlling the grade of thrombocytopenia and truly realizing the individualized dosage.

There are some limitations in the present study. For example, the sample size was not large enough, the follow-up duration was short, there was a lack of evaluation on the quality of life of patients after chemotherapy, and the possible influence of the different cycles of chemotherapy on the efficacy in both groups was not studied. In the future, therefore, large-sample prospective multicenter randomized controlled studies remain to be conducted to evaluate the application value of lobaplatin in the chemotherapy of extensive-stage SCLC more completely and accurately, so as to provide references for selecting the chemotherapy regimens for extensive-stage SCLC in the clinic.

Conclusions

The short-term efficacy of EL and EP regimens is equivalent in the first-line treatment of extensive-stage SCLC, both OS and PFS are similar, and the adverse reactions can be tolerated. The EL regimen has mild gastrointestinal reactions, and is worthy of clinical popularization.

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Conflict of interests

The authors declare no conflict of interests.

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