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ORIGINAL ARTICLE

Retrospective study of the efficacy and toxicity of lobaplatin-etoposide chemotherapy in small cell lung cancer

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Abstract

Background: A retrospective study was conducted to assess the efficacy and toxicity of lobaplatin-etoposide (EL) chemotherapy for small cell lung cancer (SCLC).

Methods: The clinical data of 50 patients treated in our department from May 2014 to March 2018 were obtained. Untreated patients with SCLC administered LBP intravenously (IV) at 30 mg/m^2 on day 1 and etoposide IV at 100 mg/m^2 on days 1, 2, and 3 were enrolled. The treatment was cycled every 21 days.

Results: The median overall and progression-free survival rates of the 50 patients were 11.67 (range: 7.30–16.04) and 6.8 (range: 5.25–8.35) months, respectively, with an overall response rate of 66% and a disease control rate of 90%. The most frequent drug-related adverse effects were leukopenia and neutropenia, and no grade 3/4 hepatotoxicity or nephrotoxicity was observed.

Conclusion: These results indicate that LBP-containing chemotherapy is effective and tolerable for SCLC in terms of response and survival.

Introduction

Lung cancer is the most common malignant tumor in the world, with the highest morbidity and mortality. There are approximately 1.8 million new cases of lung cancer and 1.59 million deaths worldwide each year.[1] Small cell lung cancer (SCLC) accounts for approximately 15% of lung cancer cases.[2] SCLC has a high degree of malignancy, and biological features, such as distant metastasis and recurrence, easily occur.[3] Approximately two thirds of SCLC patients are diagnosed as extensive, and as reported, the median survival of extensive small cell lung cancer (ES-SCLC) patients without treatment is only 2–4 months, with a one-year survival rate of approximately 2%.[4]

Less than 5% of patients are in clinical stage I ($T_{1\text{-}2}N_0M_0$) and can benefit from surgery.[5,6] Chemotherapy is the most important treatment for untreated SCLC patients ineligible for radical surgery.[4] The platinum-based drug and etoposide regimen is the most commonly used chemotherapy.[7] The severe side effects of cisplatin, such as gastrointestinal toxicity, nephrotoxicity, and neurotoxicity, affect its clinical application. Lobaplatin (LBP) is a third-generation platinum anticancer drug that has anticancer activity similar to that of cisplatin. It has shown promising activity in several preclinical studies, with incomplete cross-resistance with other platinum drugs and lower renal toxicity than cisplatin.[8] In the Chinese Society of Clinical Oncology (CSCO) guidelines for the diagnosis and treatment of primary lung cancer (2016.V1), the LBP combined with etoposide (EL) regimen was recommended as a first-line option (Category 2A evidence) for ES-SCLC. However, some oncologists are concerned about toxicity, especially grade 3/4 thrombocytopenia, for the treatment of SCLC. Therefore, we conducted a retrospective study on the efficacy and toxicity of EL chemotherapy in SCLC.

Methods

Patient selection

Fifty-four patients histologically diagnosed with SCLC and treated with EL from May 2014 to March 2018 at the Medical Oncology Department, Tianjin Medical University General Hospital were enrolled in the study. Four patients were excluded from our analysis because they had been

treated with EL but an evaluation of efficacy and toxicity had not been made.

Research methods

We reviewed and followed up the patients by consulting medical records, via telephone conversation, and so on. Clinical data, including age, gender, smoking status, Eastern Cooperative Oncology Group performance status (ECOG PS), Veterans Administration Lung Group (VALSG) stage (limited/extensive), metastatic site (bone), first-line chemotherapy cycle, thoracic radiation therapy, and second-line chemotherapy, were collected. Clinical responses were defined according to Response Evaluation Criteria in Solid Tumors, version 1.1.[9] Progression-free survival (PFS) was determined from the date of commencing primary systemic therapy to the date of disease progression or death from any cause. Overall survival (OS) was calculated from the date of commencing primary systemic therapy to the date of death or the last follow-up (31 July 2018).

Statistical analyses

Kaplan–Meier curves were used to evaluate PFS and OS, which were compared using the log-rank test. Median values and 95% confidence intervals (CIs) were also reported. Univariate and multivariate analyses were performed using Cox proportional hazards regression models. Only factors with a $P < 0.05$ were included in multivariate analysis. All statistical analyses were conducted using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

Results

Fifty patients were treated with EL in this study. The median follow-up period was 12.2 months. The median patient age was 63 (range: 47–81) years at the commencement of EL treatment. Thirty-eight patients were male, 43 patients had a history of smoking, 41 patients had an ECOG PS of 0–1, 35 (70%) patients were in extensive stage, the median number of EL treatment cycles was 4.58, and 8 patients had accompanying bone metastasis (Table 1).

Table 1 Baseline patient characteristics

Characteristics	N	
Median age (range) (years)	63 (47–81)	%
Age (< 65/≥ 65)	28/22	56%/44%
Gender (male/female)	38/12	76%/24%
Smoking history (smoker/non-smoker)	43/7	86%/14%
ECOG PS (0–1/≧2)	41/9	82%/18%
VALSG stage (limited/extend)	15/35	30%/70%
First-line chemotherapy cycles (< 4/≧4)	17/33	34%/66%
Thoracic radiation therapy (yes/no)	20/30	40%/60%
Second-line chemotherapy (yes/no)	23/27	46%/54%

ECOG PS, Eastern Cooperative Oncology Group performance status; VALSG, Veterans Administration Lung Group stage.

The overall response rate (ORR) and disease control rate (DCR) were 66% and 90%, respectively. However, when we considered patients separately by stage, the ORR and DCR were 86% and 100% for limited stage, and 54% and 93.3% for extensive stage, respectively (Figs 1,2). The median PFS of all patients was 6.8 (95.0% confidence interval [CI] 5.248–8.352) months (Fig 3a,b). The median PFS rates at different stages (limited vs. extensive: 9.6 [95% CI 5.85–13.35] vs. 5.9 [95% CI 5.25–8.35] months; $P < 0.05$) (Fig 3c) were significantly different.

Kaplan–Meier curves of OS are shown in Figure 4. The median OS of all patients was 11.67 (95% CI 7.30–16.04) months (Fig 4a). There were no differences in median OS according to age, smoking status, gender, PS, or receipt of second-line therapy. The median OS rates of different stages (limited vs. extensive: unreached vs. 9.4 [95% CI 6.45–12.34] months; $P < 0.05$) (Fig 4b), the number of first-line chemotherapy cycles (≧ 4 vs. < 4: 12.7 [95% CI 9.63–12.31] vs. 5.1 [95% CI 1.15–8.98] months; $P < 0.05$) (Fig 4c), and whether thoracic radiation was administered (yes vs. no: 14.3 [95% CI 13.64–14.96] vs. 7.8 [95% CI 6.57–8.97] months; $P < 0.05$) (Fig 4d) were significantly different.

A univariate Cox proportional hazards regression model of OS in EL-treated patients with SCLC was performed. The following variables were not correlated: gender, age, smoking status, performance status, number of first-line chemotherapy cycles, and receiving second-line therapy (Fig 4e). Only thoracic radiation was correlated with OS.

Safety

The most common grade 3/4 adverse events were leukopenia, neutropenia, anemia, and anorexia (Table 2). Grade 3 or 4 leukopenia (36%), neutropenia (62%), and hypohemia (12%) were frequent, and neutropenia (62%) was much more common than reported in historical studies. The incidence of grade 3/4 thrombocytopenia was substantially decreased compared to the results of previous studies. Non-hematologic toxicities were tolerable, with the most severe being debilitation (grade 3/4, 6%). We compared the absolute dosage of LBP in the first leukopenia appearance, and there was no difference between grades 1/2 and 3/4 (104.5 [95% CI 80.35–128.7] mg and 92.27 [95% CI 50.82–133.7] mg, respectively; $P > 0.05$) (Fig 5). The same results were obtained for the relationship between

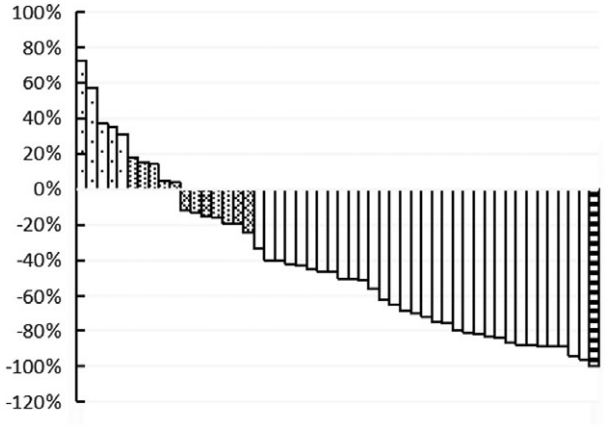

Figure 1 The overall tumor shrinkage rate. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. ▨ PD, ■ SD, ▭ PR, ▤ CR.

leukopenia degree and the number of chemotherapy cycles (grade 1/2 vs. 3/4: 2.2 vs. 1.8; $P > 0.05$) (Fig 6). Bone metastasis and PS status were risk factors in both groups (Table 3). Neither unexpected serious adverse events nor death occurred as a result of the treatment.

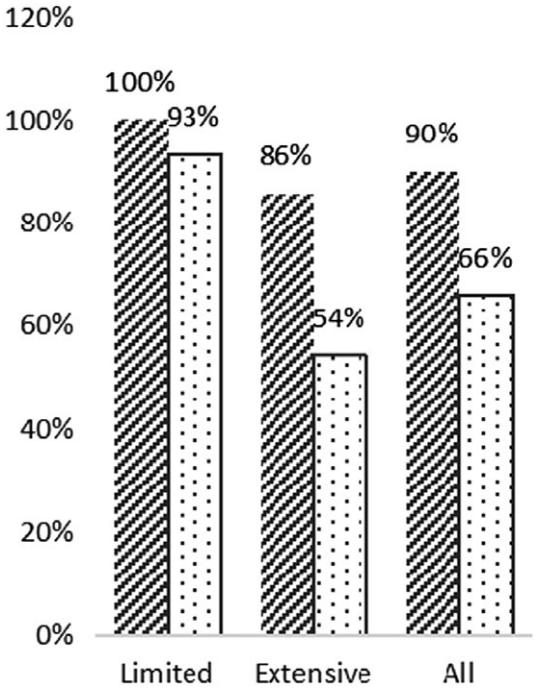

Figure 2 The disease control rate (DCR) and overall response rate (ORR) at different stages. ▨ DCR, ▨ ORR.

Discussion

Lobaplatin is a third-generation platinum anticancer drug. It has various advantages, including potent antineoplastic activities, no significant nephrotoxicity or neurotoxicity, and no cross-resistance with cisplatin.[10–13] It has anti-cancer activity in lung cancer,[14] hepatocellular carcinoma,[15] breast cancer,[16] and metastatic nasopharyngeal cancer.[17,18]

The outcomes for SCLC patients, especially for ES-SCLC patients, are often dismal, with median OS of < 10 months and five-year survival of < 5%.[19] Currently, the choice of first-line treatment for SCLC is four to six cycles of etoposide combined with a platinum-based drug (cisplatin or carboplatin), which results in median survival of 8–10 months.[20] Combination chemotherapy with irinotecan and cisplatin for SCLC leads to equal or better survival than etoposide and cisplatin, with median survival of 9.3–12.8 months.[21,22] A phase III study of EL in ES-SCLC patients and other studies on the EL regimen reported median PFS and DCR of 4.7–6.5 months and 69.5–90.4%, respectively, in first-line treatment.[23–26] Our results are consistent with the findings of these studies. The median PFS and DCR in our study cohort were 6.8 months and 90% in all patients (limited vs. extensive stage: 9.6 vs. 5.9 months, 100% vs. 84%, respectively). The median OS for first-line patients was 11.3 months. Our results show that the EL regimen is equal to previous standard regimens in terms of OS in SCLC. However, if we divide the patients into two groups by VALSG stage, the OS was only 9.6 months for ES-SCLC, which is lower than reported in previous studies. OS was not reached in the LD-SCLC group.

Myelosuppression is the main toxicity of LBP. Jiang *et al.* reported that 57 patients with SCLC were treated with single-drug LBP chemotherapy, and the incidence of grade 3/4 thrombocytopenia was 11.9%.[27] In previous studies, reports of grade 3/4 thrombocytopenia, neutropenia, and anemia after EL treatment were 8.7–26.7%, 17.9–56.7%, and 0–21%, respectively.[23–25,28]

Thrombocytopenia is the most concerning adverse reaction to oncologists because patients are very slow to recover and in some patients it is necessary to postpone chemotherapy or decrease the dosage. In our study, the prevalence of grade 3/4 thrombocytopenia was only 6%, which is apparently lower than reported in previous publications (8.7–26.7%). The neutropenia rate (82%) in our study was the highest compared to all previous studies of LBP, and the prevalence of grade 3/4 neutropenia was 62%. We conducted further analysis of neutropenia and found that there was no difference between grades 1/2 and 3/4 in regard to chemotherapy cycle number and the absolute dose of LBP; that is, there was no correlation between the neutropenia degree (the first appearance) and the LBP dose. No other studies have reported this

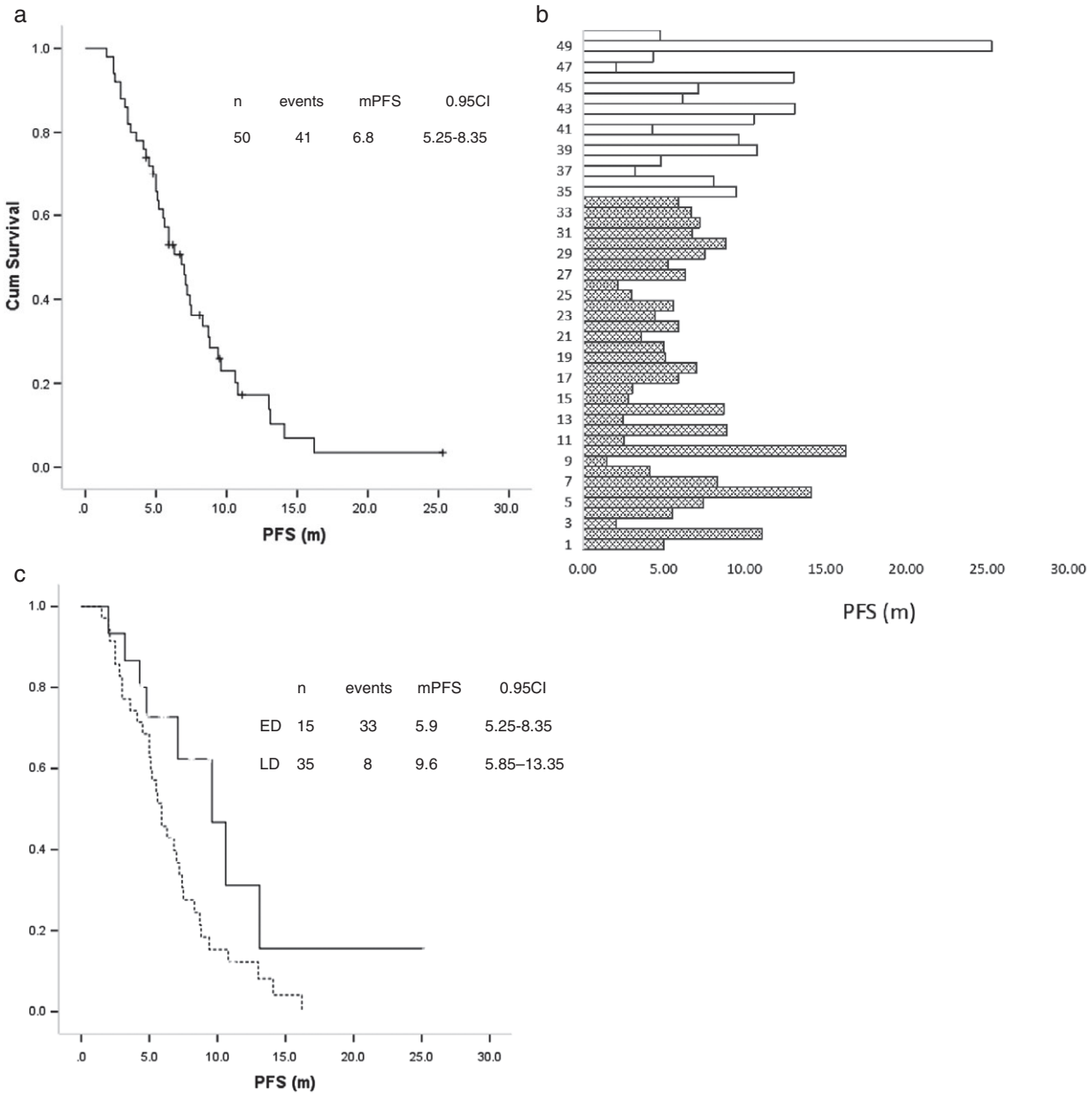

Figure 3 (**a**) Kaplan–Meier curve and (**b**) bar diagram of progression-free survival (PFS) of small cell lung cancer (SCLC) patients treated with lobaplatin-etoposide (EL). ▭ Extensive stage, ▨ limited stage. (**c**) Kaplan–Meier curve of PFS of SCLC patients treated with EL at different stages. ⌐¬ limited, ⌐¬ extend. CI, confidence interval.

finding. All patients treated with chemotherapy are at risk of developing neutropenia, but it is difficult for oncologists to predict which patients or population of patients is clearly at greater risk. A previous review found many of the same risk factors as our study, including age and PS.[29] Age itself is a general risk factor for the development of severe or febrile neutropenia, but it may also be associated with other patient characteristics that affect the risk.[30] In some studies, poor PS (e.g. World Health Organization grade > 1) as a measure of frailty, or bone or bone marrow metastases, have been reported as significant risk factors.[31] We reached the same conclusion (Table 4). The risk of neutropenia has also been associated with the phase of therapy, with the perhaps counter-intuitive but well supported conclusion that the greatest risk is in the earliest cycles. Just as in our review, 75.6% of neutropenia cases appeared in the first two cycles. Studies have shown the predictive value of the first-cycle

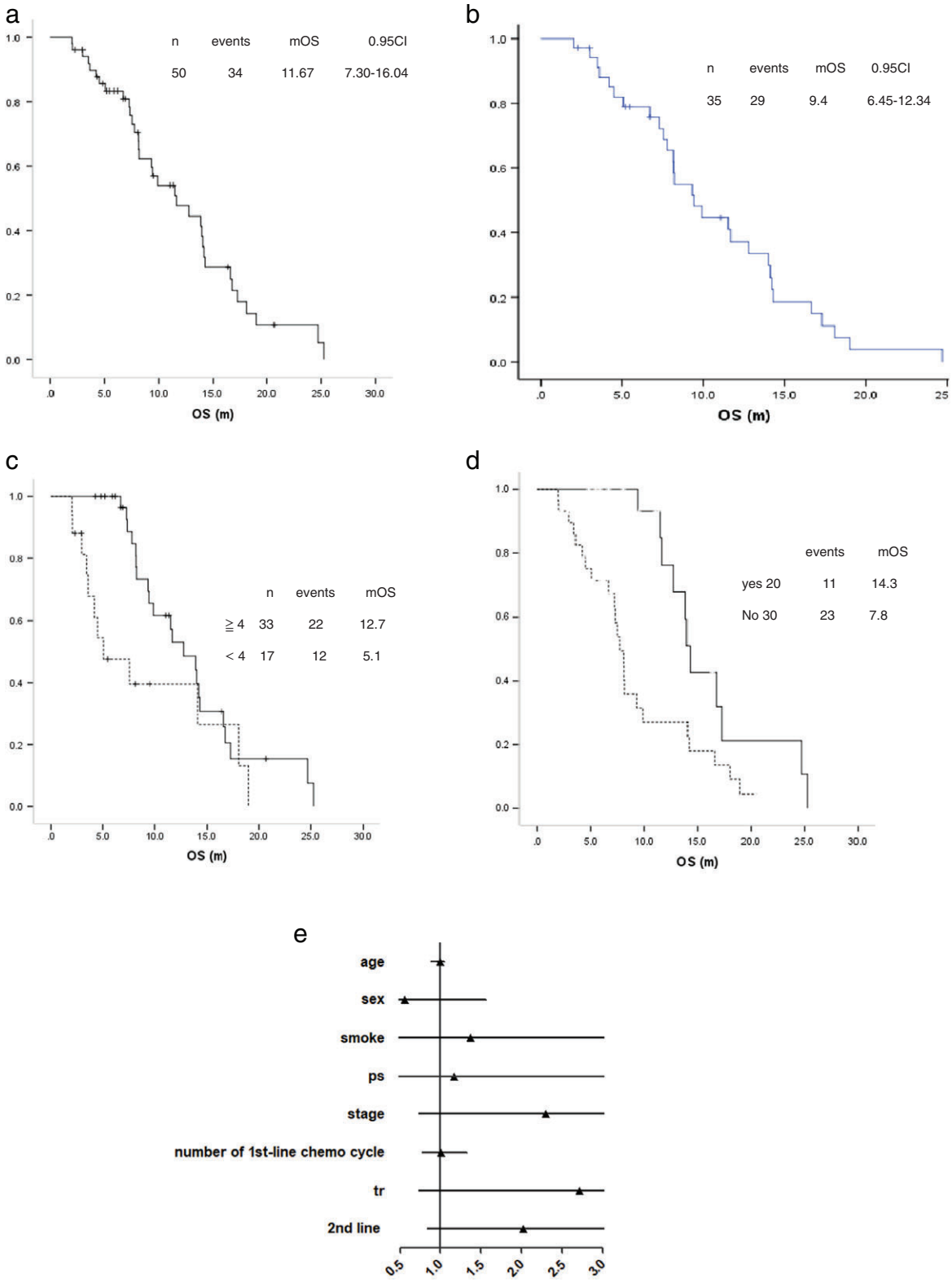

Figure 4 Kaplan–Meier curves of (**a**) overall survival (OS) and (**b**) median (m)OS of small cell lung cancer (SCLC) patients treated with lobaplatin-etoposide (EL), and (**c**) OS of EL-treated patients. ⎽⎽⌐¬ ≥4, ⎽⎽⌐¦ <4, ⎽⎽⌐¬ ≥4-censored, ⎽⎽⌐¦ <4-censored. (**d**) Kaplan–Meier curve of mOS for patients with SCLC administered radiation. —|— yes, --|-- no. (**e**) Correlation of different factors and OS. CI, confidence interval; PS, performance status; Tr, thoracic radiation.

Table 2 Adverse events in all EL-treated patients

	Grade					Grade 1–4		Grade 1/2		Grade 3/4		
Toxicity	0	1	2	3	4	N	%	N	%	N	%	History
Hematologic toxicity												
Leukopenia	11	6	15	16	2	39	78%	21	42%	18	36%	17.4–50.5%
Neutropenia	9	3	7	17	14	41	82%	10	20%	31	62%	25.80%
Hypohemia	30	9	5	6	0	20	40%	14	28%	6	12%	4.5–21.7%
Thrombocytopenia	36	1	8	3	2	14	24%	9	18%	5	6%	9.1–19.9%
GI toxicity												
Nausea	27	13	8	2	0	23	46%	21	42%	2	4%	
Vomiting	42	4	3	1	0	8	16%	7	14%	1	2%	
Astriction	43	6	1	0	0	7	14%	7	14%	0	0%	
Anorexia	35	12	2	1	0	15	30%	14	28%	1	2%	
Diarrhea	50	0	0	0	0	0	0%	0	0%	0	0%	
Other toxicity												
Debilitation	20	19	8	3	0	30	60%	27	54%	3	6%	
Alopecia	27	12	10	1	0	23	46%	22	44%	1	2%	
Hepatotoxicity	46	4	0	0	0	4	8%	4	8%	0	0	
Nephrotoxicity	50	0	0	0	0	0	0	0	0	0	0	

EL, lobaplatin-etoposide; GI, gastrointestinal.

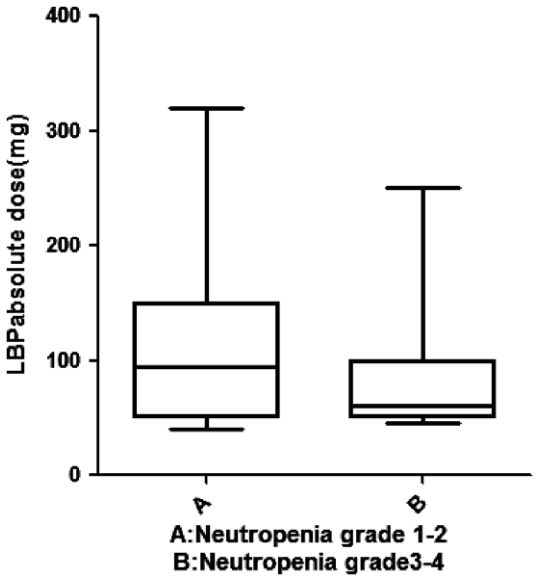

Figure 5 The absolute dosage of lobaplatin (LBP) when the first incidence of neutropenia was a different grade ($P > 0.05$).

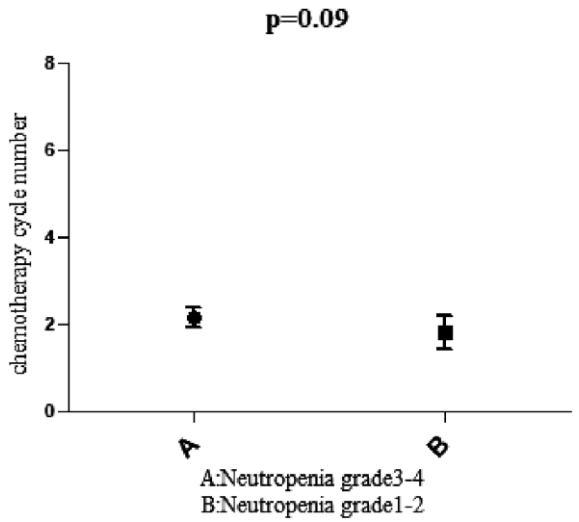

Figure 6 The average number of cycles of EL when the first incidence of neutropenia was a different grade ($P > 0.05$).

nadir in leukocyte counts and decreases in hemoglobin levels for predicting neutropenic complications in later cycles.[32,33]

There are several limitations to this study. First, given the retrospective nature of its design, there is potential for bias. Second, because of the small sample size, further OS data of limited stage patients is needed to draw a final conclusion.

Table 3 Comparison of risk factors at different grades of neutropenia

Neutropenia	All grades	Grade 1/2	Grade 3/4	*P*
Median age		63.1	64.5	> 0.05
Bone metastasis	8/41	0/10	8/31	< 0.05
Occurred in the first two cycles	31/41	8/10	23/31	> 0.05
PS 0–1/≧ 2	36/5	9/1	27/4	< 0.05

PS, performance status.

In summary, our results suggest that the EL regimen is effective and well tolerated in SCLC patients as first-line treatment.

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Disclosure

No authors report any conflict of interest.

References

1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87–108.
2 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**: 5–29.
3 Sabari JK, Lok BH, Laird JH, Poirier JT, Rudin CM. Unravelling the biology of SCLC: Implications for therapy. *Nat Rev Clin Oncol* 2017; **14**: 549–61.
4 Zhang X, Yu J, Zhu H *et al.* Consolidative thoracic radiotherapy for extensive stage small cell lung cancer. *Oncotarget* 2017; **8**: 22251–61.
5 Takei H, Kondo H, Miyaoka E *et al.* Surgery for small cell lung cancer: A retrospective analysis of 243 patients from Japanese Lung Cancer Registry in 2004. *J Thorac Oncol* 2014; **9**: 1140–5.
6 Kahnert K, Kauffmann-Guerrero D, Huber RM. SCLC-state of the art and what does the future have in store? *Clin Lung Cancer* 2016; **17**: 325–33.
7 Kalemkerian GP. Staging and imaging of small cell lung cancer. *Cancer Imaging* 2011; **11**: 253–8.
8 Fruh M, De Ruysscher D, Popat S, Crino L, Peters S, Felip E. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24**: 99–105.
9 McKeage MJ. Lobaplatin: a new antitumour platinum drug. *Expert Opin Investig Drugs* 2001; **10**: 119–28.
10 Wheate NJ, Walker S, Craig GE, Oun R. The status of platinum anticancer drugs in the clinic and in clinical trials. *Dalton Trans* 2010; **39**: 8113–27.
11 Ali I, Wani WA, Saleem K, Haque A. Platinum compounds: A hope for future cancer chemotherapy. *Anticancer Agents Med Chem* 2013; **13**: 296–306.
12 Saris CP, Van De Vaart PJ, Rietbroek RC, Blommaert FA. In vitro formation of DNA adducts by cisplatin, lobaplatin and oxaliplatin in calf thymus DNA in solution and in cultured human cells. *Carcinogenesis* 1996; **17**: 2763–9.
13 Liang YF, Sui DH, Cheng Y. Clinical research progress of the new antitumor drug lobaplatin in the treatment of small cell lung cancer. *Chin J New Drugs* 2014; **23**: 184–8 209.
14 Xie CY, Xu YP, Jin W, Lou LG. Antitumor activity of lobaplatin alone or in combination with antitubulin agents in non-small-cell lung cancer. *Anticancer Drugs* 2012; **23**: 698–705.
15 ZhouB SH, Zhu KS *et al.* Chemoembolization with lobaplatin mixed with iodized oil for unresectable recurrent hepatocellular carcinoma after orthotopic liver transplantation. *J Vasc Interv Radiol* 2010; **21**: 333–8.
16 Deng QQ, Huang XE, Ye LH, Lu YY, Liang Y, Xiang J. Phase II trial of Loubo(R) (Lobaplatin) and pemetrexed for patients with metastatic breast cancer not responding to anthracycline or taxanes. *Asian Pac J Cancer Prev* 2013; **14**: 413–7.
17 Zhang S, Chen J, Yang S, Lin S. An open-label, single-arm phase II clinical study of docetaxel plus lobaplatin for Chinese patients with pulmonary and hepatic metastasis of nasopharyngeal carcinoma. *Anticancer Drugs* 2016; **27**: 685–8.
18 Long GX, Lin JW, Liu DB *et al.* Single-arm, multi-centre phase II study of lobaplatin combined with docetaxel for recurrent and metastatic nasopharyngeal carcinoma patients. *Oral Oncol* 2014; **50**: 717–20.
19 Nicholson AG, Chansky K, Crowley J *et al.* The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2016; **11**: 300–11.
20 Roth BJ, Johnson DH, Einhorn LH *et al.* Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: A phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol* 1992; **10**: 282–91.
21 Noda K, Nishiwaki Y, Kawahara M *et al.* Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002; **346**: 85–91.
22 Hanna N, Bunn PA Jr, Langer C *et al.* Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol* 2006; **24**: 2038–43.
23 Cheng Y, Fan Y, Liu X *et al.* A randomized, multicenter phase III study of lobaplatin/etoposide versus cisplatin/etoposide as first-line therapy in patients with extensive-stage small-cell lung cancer and circulating tumor cells (CTCs) as an exploratory biomarker. *J Clin Oncol* 2014; **32**: 7595.
24 Chen TJ, Gao F, Sun ZM *et al.* Comparative study of lobaplatin and cisplatin combined with etoposide for advanced small cell lung cancer. *J Xian Jiaotong Univ* 2013; **34**: 198–201.

25 Guo W, Liao G, Gao H *et al*. Randomized comparison of lobaplatin plus etoposide and cisplatin plus etoposide chemotherapy in patients with extensive-stage small cell lung cancer. *The Chinese-German Journal of Clinical Oncology* 2013; **12**: 365–8.
26 Zhou NN, Zhao YY, Zhai LZ *et al*. The efficacy and toxicity of lobaplatin-contained chemotherapy in extensive-stage small-cell lung cancer. *J Cancer* 2018; **9**: 2232–6.
27 Jiang W, Lin T, Xu R *et al*. A pilot study of Lobaplatin as a single agent in the treatment of lung cancer. *Zhejiang Cancer Journal* 1998; **4**: 241–2.
28 Zhuo YL, Li SY, Zhao CQ *et al*. Clinical efficacy of etoposide plus lobaplatin therapy for extensive stage small cell lung cancer. *Shandong Med* 2012; **14**: 61–2.
29 Wilson-Royalty M, Lawless G, Palmer C, Brown R. Predictors for chemotherapy-related severe or febrile neutropenia: A review of the clinical literature. *J Oncol Pharm Pract* 2001; **7**: 141–7.
30 Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: Risks, consequences, and new directions for its management. *Cancer* 2004; **100**: 228–37.
31 Wang SH, Wu YQ, Wang YF. Cheng P. *The analysis of influencing factors in bone marrow suppression after chemotherapy. J Jilin Medical* 2014; **18**: 4010–1.
32 Blay JY, Chauvin F, Le Cesne A *et al*. Early lymphopenia after cytotoxic chemotherapy as a risk factor for febrile neutropenia. *J Clin Oncol* 1996; **14**: 636–43.
33 Silber JH, Fridman M, DiPaola RS, Erder MH, Pauly MV, Fox KR. First-cycle blood counts and subsequent neutropenia, dose reduction, or delay in early-stage breast cancer therapy. *J Clin Oncol* 1998; **16**: 2392–400.

