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/m² on day 1 and etoposide IV at 100 mg/m² 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. Small cell lung cancer (SCLC) accounts for approximately 15% of lung cancer cases. SCLC has a high degree of malignancy, and biological features, such as distant metastasis and recurrence, easily occur. 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%.

Less than 5% of patients are in clinical stage I (T1N0M0) and can benefit from surgery. Chemotherapy is the most important treatment for untreated SCLC patients ineligible for radical surgery. The platinum-based drug and etoposide regimen is the most commonly used chemotherapy. 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. 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).

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 was 86% and 100% for limited stage, and 54% and 93.3% for extensive stage, respectively (Figs 1,2). The median PFS rates at different stages (limited vs. extensive) were 9.6 [95% CI 5.85–13.35] vs. 5.9 [95% CI 5.25–8.35] months; P < 0.05) (Fig 3a). The same results were obtained for the relationship between the occurrence of grade 3 or 4 leukopenia appearance, thrombocytopenia, 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.

**Table 1 Baseline patient characteristics**

| Characteristics                                      | N     | %     |
|------------------------------------------------------|-------|-------|
| Median age (range) (years)                           | 63 (47–81) | 56%|44%|
| Gender (male/female)                                 | 38/12 | 76%|24%|
| Smoking history (smoker/non-smoker)                  | 43/7  | 86%|14%|
| ECOG PS (0–1/2/22)                                   | 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 therapy (yes/no)            | 23/27 | 46%|54%|
| ECOG PS, Eastern Cooperative Oncology Group performance status; VALSG, Veterans Administration Lung Group stage.

**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...
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.

**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.
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. 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. 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. We reached the same conclusion (Table 4). The risk of neutropenia has also been associated with the phase of therapy, with the perhaps counterintuitive 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 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.
**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. (d) Kaplan–Meier curve of mOS for patients with SCLC administered radiation.  

**Notes:** CI, confidence interval; PS, performance status; Tr, thoracic radiation.
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 2  Adverse events in all EL-treated patients

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

EL, lobaplatin-etoposide; Gl, gastrointestinal.

### 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 0–1/2/3 | 36/5       | 9/1       | 27/4      | < 0.05 |

PS, performance status.

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**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).
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.

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