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Original Article

Retrospective Clinical Study on Integrated Chinese and Western Medicine in Treatment of Limited-Stage Small-Cell Lung Cancer*

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ABSTRACT **Objective:** To investigate the efficacy of integrated Chinese and Western medicine extending the progression-free survival (PFS) and overall survival (OS) of limited-stage small-cell lung cancer (LS-SCLC) patients after the first-line chemoradiotherapy. **Methods:** The data of 67 LS-SCLC patients who received combined treatment of Chinese medicine (CM) and Western medicine (WM) between January 2013 and May 2020 at the outpatient clinic of Guang'anmen Hospital were retrospectively analyzed. Thirty-six LS-SCLC patients who received only WM treatment was used as the WM control group. The medical data of the two groups were statistically analyzed. Survival analysis was performed using the product-limit method (Kaplan–Meier analysis). The median OS and PFS were calculated, and survival curves were compared by the Log rank test. The cumulative survival rates at 1, 2, and 5 years were estimated by the life table analysis. Stratified survival analysis was performed between patients with different CM administration time. **Results:** The median PFS in the CM and WM combination treatment group and the WM group were 19 months (95% CI: 12.36–25.64) *vs*. 9 months (95% CI: 5.96–12.04), respectively, HR=0.43 (95% CI: 0.27–0.69, *P*<0.001). The median OS in the CM and WM combination group and the WM group were 34.00 months (95% CI could not be calculated) *vs*. 18.63 months (95% CI: 16.43–20.84), respectively, HR=0.40 (95% CI: 0.24–0.66, *P*<0.001). Similar results were obtained in the further stratified analysis of whether the duration of CM administration exceeded 18 and 24 months (*P*<0.001). **Conclusion:** The combination treatment of CM and WM with continuing oral administration of CM treatment after the first-line chemoradiotherapy for LS-SCLC patients produced better prognosis, lower risks of progression, and longer survival than the WM treatment alone. (Registration No. ChiCTR2200056616)

KEYWORDS limited-stage small cell lung cancer, combination of Chinese and Western medicine, overall survival, progression-free survival, Chinese medicine

Lung cancer is the leading cause of cancer deaths worldwide, with an estimated 2.1 million new cases and 1.8 million deaths in 2018. Small-cell lung cancer (SCLC) accounts for an estimated 250,000 new cases and at least 200,000 deaths worldwide each year.[1] SCLC accounts for approximately 15% to 20%[2,3] of new lung cancers and 25% of lung cancer deaths and is characterized by a high malignancy, rapid progression, early and high probability of distant metastasis, high likelihood of recurrence, and acquired drug resistance. SCLC is the most malignant type of lung cancer, with an extremely poor prognosis, a median survival for untreated patients of only 2 to 4 months,[4] and a 5-year survival rate of less than 5%.[5,6] In most cases, metastases have already occurred at the time of diagnosis, with only 40% in the limited stage and 60% in the extensive stage.[7] Statistics between 1983–2012 showed that the median survival of SCLC was only 7 months.[8] Recently it has been shown that the median survival of limited-stage

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small-cell lung cancer (LS-SCLC) patients receiving chemoradiotherapy was 16 to 24 months, while the median survival for extensive-stage patients remains 7 to 12 months. Currently, though evaluations have been made for novel chemotherapy regimens and several biological agents by CT screening and many clinical trials, no significant improvement has been observed in the overall survival (OS) rates, and no improvement has been made regarding the prognosis of SCLC.[9,10]

For LS-SCLC at early stages, $T_{1\text{-}2}N_0M_0$, surgery is an important component of the comprehensive treatment. However, only 5%[11] of patients meet the criteria for surgery. For most LS-SCLC cases, platinum-based chemotherapy with etoposide combined with concurrent chest radiotherapy is the current standard treatment,[12] with a median OS of 16–24 months. For patients unable to tolerate concurrent radiotherapy, sequential chemoradiotherapy is often administered, with a median OS and 5-year survival rate after treatment of 14.0–19.7 months and 20%, respectively.[13] The risk of brain metastases has been reduced by prophylactic cranial irradiation (PCI) in patients with effective primary treatment. Currently, regular follow-ups are performed for most LS-SCLC patients after the standard first-line treatment by Western medicine (WM). No effective follow-up treatment has been developed to prevent recurrence and metastasis. Despite the development of several novel cytotoxic drugs, targeted therapies, and immunotherapeutic agents, slow progression has been made towards effective SCLC treatment.[15]

SCLC is highly sensitive to chemoradiotherapy. However, due to the highly malignant cancer cells with rapid growth, treatment frequently fails due to swift recurrence and metastasis. In addition, the tumors generally developed resistance to initial drugs, rendering poorer outcomes during subsequent treatments and resulting in a short OS. Therefore, the high recurrence and metastasis rate, as well as the short survival after the standard WM treatment for SCLC, remain urgent medical issues that require solutions, new treatment methods, and effective protocols. Chinese medicine (CM), as an alternative therapy for malignant tumors, is increasingly applied in the comprehensive treatment of tumors. This current retrospective analysis aimed to investigate the efficacy of integrated Chinese and Western medicine in extending the survival of LC-SCLC patients.

METHODS

Diagnostic Criteria

Diagnoses of SCLC were made according to the "National Comprehensive Cancer Network (NCCN) guidelines".[16] Pathological diagnosis was required for every patient receiving treatment. Metastases (limited-stage or extensive-stage) staging criteria were based on the "Veterans Administration Lung Study Group (VALG) guidelines" for SCLC.[17] In CM, SCLC patients were divided into four syndrome types, including Fei (Lung) and Pi (Spleen) qi deficiency, turbid phlegm and blood stasis, heat toxin obstructing Fei, and qi and yin deficiency syndromes according to the "Clinical practice guidelines of Chinese medicine in oncology" (Appendix 1).[18]

Inclusion and Exclusion Criteria

Inclusion criteria for participants in the combination CM and WM treatment group were: (1) patients aged 18 to 75 years; (2) LS-SCLC patients (metastases staging criteria were based on the VALG guidelines[17]) who had a clear pathological diagnosis and received standard treatment following the NCCN clinical guidelines, such as chest radiotherapy, chemotherapy, or PCI; (3) a survival duration >3 months; and (4) received CM treatment for ⩾6 months.

The exclusion criteria were: (1) multiple serious comorbidities, such as of the heart, liver, kidney, or the hematopoietic system; (2) patients suffering from other kinds of primary malignant tumors; (3) pregnant women or psychiatric patients; (4) patients who had participated in other clinical trials of novel drugs; and (5) patients missing basic information.

The study was approved by the Ethic Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (Approval No. 2021-004-KY-01), and the protocol has been registrated at ClinicalTrials.gov (No. ChiCTR2200056616).

Patient Selection and Data Collection

A total of 67 patients who received combined CM and WM treatment between January 2013 and May 2020 were selected for retrospective analysis as the treatment group (Figure 1). The medical records were obtained from the outpatient clinic of Guang'anmen Hospital. For analysis and comparison, patients who only received the WM

treatment were matched as the WM treatment group. Their medical records were obtained from the outpatient clinic of Henan Cancer Hospital between December 2017 and May 2019. To collect survival information, patients in both groups were followed up with, and the last follow-up date was May 1, 2021.

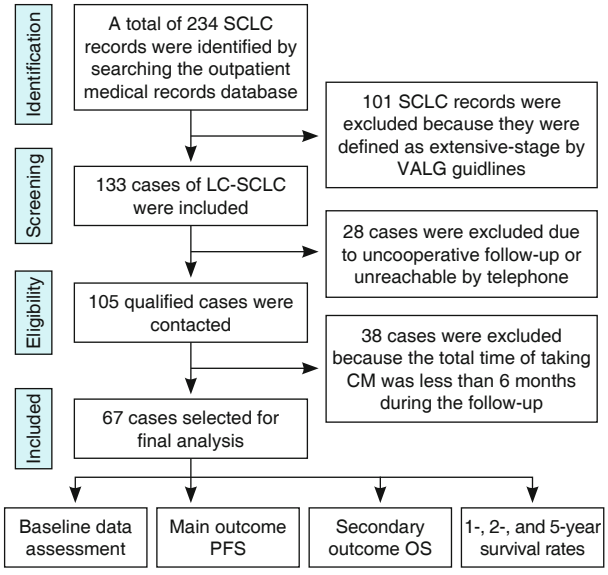

Figure 1. Flow Diagram of Inclusion and Follow-up Process

Notes: SCLC: small-cell lung cancer; LC: limited stage VALG: Veterans Adninistration Lung Study Group; CM: Chinese medicine; PFS: progress free survival; OS: overall survival

The following clinical information was collected from patients: gender; age; smoking history; Karnofsky Performance Scale score; type of pathology; clinical stage (according to the VALG[17] staging criteria); interventions, including chemotherapy, radiotherapy, targeted therapy, immunotherapy, and CM treatment (including duration of oral administration, compatibility of CM, and composition of CM formulae); and patient progression. These were all factors that might be relevant to patient progression and prognosis in this study.

Treatment

All 103 patients received the standard treatment of chemotherapy (cisplatin combined with etoposide or carboplatin combined with etoposide) for 4–6 cycles, chest irradiation, and PCI according to the 2013 edition of the NCCN clinical practice guidelines for SCLC.[16]

A total of 67 patients included in the CM and WM combination treatment group were also administered oral CM decoction after the end of the first line chemoradiotherapy by WM. The treatment method was referred to "Clinical practice guidelines of Chinese medicine in oncology".[18] The treatment was based on the combination of symptoms, tongue texture, tongue coating, pulse identification, and disease identification. All Chinese herbal medicines were supplied by the Pharmacy of Guang'anmen Hospital. The treatment prescription consisted of the Chinese herbal medicine formulae based on syndrome differentiation and the anti-tumor drugs based on disease differentiation (Appendix 1).[18] All patients in the combination group took CM decoction intermittently or continuously, 200 mL twice daily, 1 h after breakfast and dinner for at least 6 months according to our experience in previous study.[19]

Efficacy Indicators

The primary endpoint was overall survival (OS), defined as the time from the date of treatment initiation to death or the study cut-off date. The secondary endpoint was progression-free survival (PFS), defined as the time from the date of treatment initiation to disease progression or death due to any cause. Other observations included the 1-, 2-, and 5-year OS rates, 1, 2, and 5-year PFS rates, stratified survival analysis of the administration of CM.

Statistical Analysis

The baseline data were analyzed using the chi-square test, and a *P*-value less than 0.05 was considered statistically significant. Survival analysis was performed using the product-limit method (Kaplan–Meier). The median OS and median PFS were calculated for each group. The survival curves and stratified survival analysis were compared by the Log rank test, and the cumulative survival rates at 1, 2, and 5 years were estimated using the life table method.

RESULTS

Patient Data

A retrospective analysis was performed on clinical data of 67 LS-SCLC patients who were included in the combination CM and WM treatment group and 36 LS-SCLC patients who only received standard WM treatment. No statistically significant difference in the baseline data was found between the two groups (*P*>0.05, Table 1). Follow-up contact was initiated for the all 103 patients on May 1, 2021.

Table 1. Comparison of Baseline Characters of LS-SCLC Patients [Case (%)]

Variable	WM group (36 cases)	CM+WM group (67 cases)	*P*-value
Female	9 (25.00)	19 (28.36)	0.715
Age			0.828
≤60 years	18 (50.00)	32 (47.76)	
>60 years	18 (50.00)	35 (52.24)	
Smoking	19 (52.78)	40 (59.70)	0.498
Western medicine treatment			
Chemotherapy	36 (100.00)	67 (100.00)	
Chest radiotherapy	36 (100.00)	67 (100.00)	
Immunotherapy or targeted therapy	3 (8.33)	7 (10.45)	0.730
Prophylactic cranial irradiation	11 (30.56)	14 (20.90)	0.276
Number of chemotherapy cycle			0.312
<6	6 (16.70)	17 (25.37)	
≤6	30 (83.30)	50 (74.63)	

Note: WM: Western medicine; the same below

Survival Curve Analysis of OS and PFS

The median OS was 34.00 months (range: 8.67–99.00) for patients in the CM and WM combination group (95% CI could not be calculated) and 18.63 months (range: 7.53–93.63) for patients in the WM treatment group (95% CI: 16.44–20.84), with significant difference between groups (HR=0.40, 95% CI: 0.24–0.66, *P*<0.001, Figure 2A).

The median PFS was 19 months (range: 3.00–99.00) for patients in the CM and WM combination group (95% CI: 12.36–25.64) and 9 months (range: 3.23–93.63) for patients in the WM treatment group (95% CI: 5.96–12.04), which were significantly different (HR=0.43, 95% CI: 0.27–0.69, *P*<0.001, Figure 2B).

Overall Survival Rates

The 1-year survival rate was 62/67 (92.47%) in the CM and WM combination group and 26/36 (72.22%) in the WM group, with significant difference between groups (HR=0.24, 95% CI: 0.08–0.72, *P*<0.05). The 2-year survival rate was 43/67 (64.86%) in the CM and WM combination group and 11/36 (30.56%) in the WM treatment group, with significant difference between groups (HR=0.38, 95% CI: 0.22–0.68, *P*<0.05). The 5-year survival rate was 36/67 (46.89%) in the CM and WM combination group and 3/36 (8.82%) in the WM treatment group, with significant difference between groups (HR=0.41, 95% CI: 0.24–0.69, *P*<0.001, Figure 3).

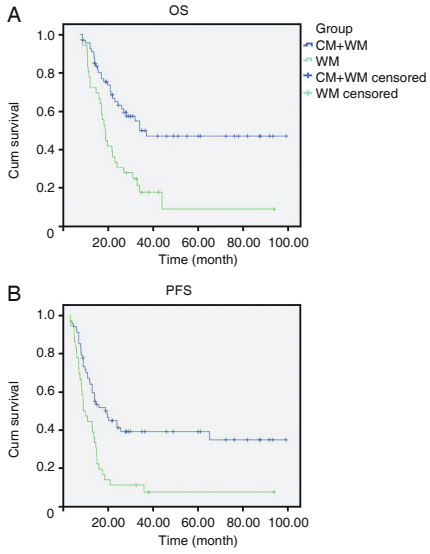

Figure 2. Comparison of OS (A) and PFS (B) of LS-SCLC Patients btween Groups

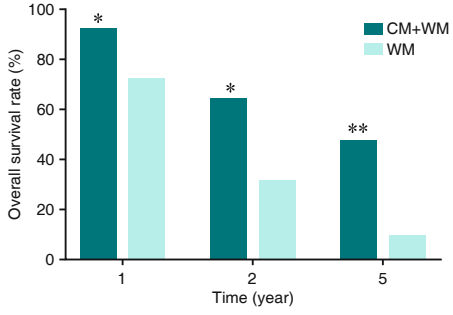

Figure 3. Comparison of 1-, 2-, and 5-Year Overall Survival Rates between Groups of LS-SCLC Patients

Notes: **P*<0.05, ***P*<0.01 vs. WM group

PFS Rates

The proportion of patients with PFS at 1-year was 43/67 (63.92%) in the CM and WM combination group and 16/36 (44.44%) in WM treatment group, which was a statistically significant difference (HR=0.52, 95% CI: 0.29–0.95, *P*<0.05). The 2-year PFS was 41.09% in the CM and WM combination group and 11.11% in the WM treatment group, which was also a statistically significant difference (HR=0.43, 95% CI: 0.27–0.70, *P*<0.001). The proportion of patients with PFS of 5-years in the CM and WM combination group was 26/67 (39.13%) and 3/36 (7.41%) in WM treatment group, which was also statistically significant (HR=0.42, 95% CI: 0.27–0.68, *P*<0.001).

Stratified Survival Analysis of Administration of Chinese Herbal Medicines

A stratified analysis of factors influencing the CM and WM treatment group was performed. It was found that the duration of CM administration

was an important survival factor. All patients in the combination CM and WM treatment group continued with CM treatment for ⩾6 months. The median duration of CM administration was 23.77 months (range: 6–90 month).

The median PFS was higher in patients taking CM for ⩾12 months, than that of patients taking CM for <12 months. There was a statistically significant difference in 2-year PFS rate between the two groups (HR=0.5, 95% CI: 0.26-0.95, *P*=0.03, Figure 4A). Similarly, the median OS was better in patients taking CM for ⩾12 months *versus* <12 months (HR=0.42, 95% CI: 0.20–0.87, *P*=0.016, Figure 4B).

Similar results were found in a stratified analysis of 18 months subgroups. The median PFS of patients taking CM for ⩾18 months was higher than that of patients taking CM for <18 months, and the difference in 2-year PFS was statistically significant (HR=0.14, 95% CI: 0.05–0.37, *P*<0.001, Figure 4C). Similarly, the median OS was better in patients taking CM for ⩾18 months. A difference in 2-year OS rate was seen between the two groups (HR=0.22, 95% CI: 0.10–0.49, *P*<0.001, Figure 4D).

The differences were more pronounced in the 24 months subgroup analysis. The median PFS was better in patients taking CM for ⩾24 months than that of patients taking CM for <24 months, with a statistically significant difference observed in 3-year survival rate between the two groups (HR=0.06, 95% CI: 0.01–0.26, *P*<0.001, Figure 4E). Similarly, the median OS in patients taking CM for ⩾24 months was better than that of patients taking CM for <24 months. The 3-year OS rate reached a statistically significant difference between the two groups (HR=0.18, 95% CI: 0.07–0.45, *P*<0.001, Figure 4F and Appendix 2).

DISCUSSION

SCLC is a specific type of lung cancer with rapid progression and a high likelihood of recurrence and metastasis.[20] Early treatment with surgery and postoperative chemoradiotherapy may result in a longer survival period for SCLC patients. Although the standard first-line treatment has an effectivity rate of up to 80%, the survival of patients with locally advanced LS-SCLC remains short, with a high likelihood of recurrence and metastasis, a discouraging prognosis. Most LS-SCLC patients experience recurrence within 6 months after the end of the first-line therapy, with a median OS of 16–24 months and a 2-year survival rate of 20%–40%.[21-23] A large-sample clinical study showed the 5-year survival rate of LS-SCLC patients receiving both chemotherapy and chest radiotherapy was 13.3%.[24] Despite decades of basic experimental and clinical research, there has been little progress in the treatment of SCLC, and patients with LS-SCLC are still prone to metastasis after radiotherapy and chemotherapy.

At present, the standard first-line treatment for SCLC chemotherapy is platinum combined with etoposide. Therapies that target molecular signaling pathways in tumor cells such as the Hedgehog signaling pathway, NOTCH signaling pathway, and

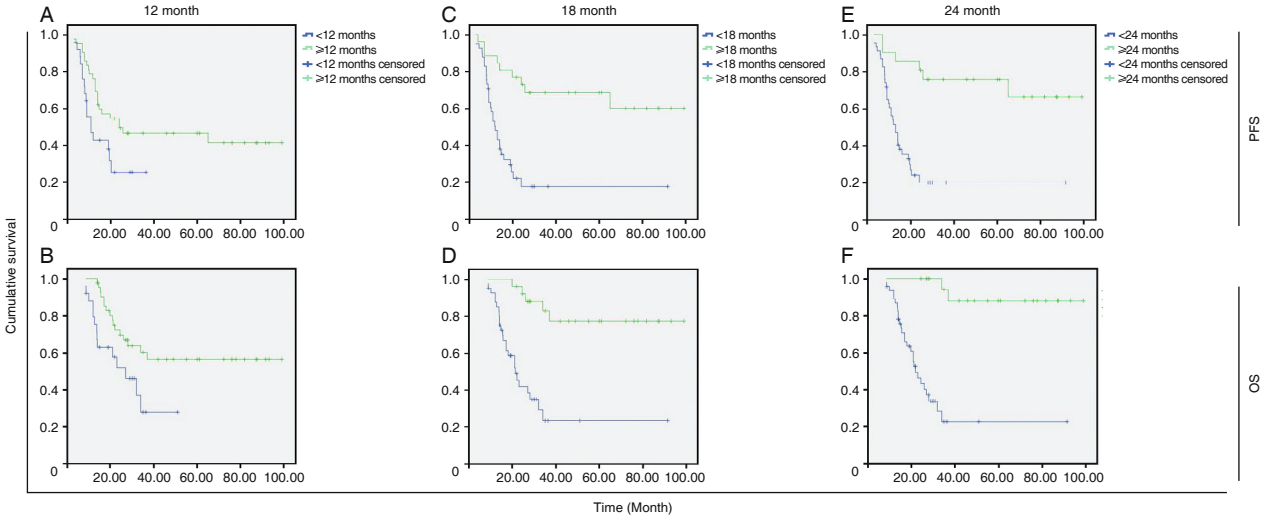

Figure 4. Stratified Survival Analysis of PFS and OS between LC-SCLC Patients with Different CM Administration Time

fibroblast growth factors are still in the research stage.[25] The clinical application of immune checkpoint inhibitors opens another window for the treatment of lung cancer. However, ongoing clinical studies indicate that immune checkpoint inhibitors can only prolong the survival of patients in a limited way. There remains no proven alternative to chemotherapy.[26] In this context, it is important to seek new treatment modalities to reduce the recurrence and metastasis of SCLC patients after radiotherapy and chemotherapy.

The preliminary clinical observations found that CM tended to reduce the recurrence and metastasis rate and extend the survival of LS-SCLC patients. A small sample clinical observation conducted by the researchers on the CM and WM combination treatment of SCLC found that the median OS of the CM and WM combination treatment was 24 months, while the cumulative survival rates at 1 and 2 years were 94.1%, 64.7% in the CM group and 80.6%, 51.6% in the WM groups, respectively. The median PFS was 19 and 14 months, respectively.[27]

The current study mainly observed the influence of CM intervention on PFS of LS-SCLC patients after WM treatment. The OS period includes the post-progressive survival (PPS), during which patients choose more treatment plans and alternative means, making it difficult to analyze the effect of CM. Therefore, in this study, PFS was selected as the main outcome indicator and OS as a secondary indicator. The results of this study were encouraging, with a PFS of 19 and 9 months, OS of 34.00 and 18.63 months, and 2-year survival rates of 64.86% and 30.56% in the CM and WM combination treatment group and the WM treatment group, respectively. The PFS and OS data in the WM treatment group were generally consistent with previous reports, which also provided a good comparison to verify the prolonged survival of patients treated with integrated CM and WM.

We were also interested in whether the duration of CM administration affected the OS of patients. Therefore, a stratified analysis of the duration of the administration of CM in the CM and WM combination treatment group was performed in this study. It was found that patients taking CM for ⩾12, ⩾18, and ⩾24 months had significantly better PFS and OS than those taking CM for <12, <18 and <24 months, respectively, suggesting that the longer patients take CM, the more they benefit in terms of PFS and OS.

The results of another clinical study with a small sample size[28] showed that the median PFS was significantly higher in SCLC patients who received CM treatment for more than 3 months than those who took CM for less than 3 months (8.7 *vs*. 4.5 months), and that the PPS was significantly longer in SCLC patients who received syndrome-based CM treatment for more than 7 months after the end of chemoradiotherapy than those who received CM treatment for less than 7 months (11.7 *vs*. 5.1 months). The above study also attempted to answer common clinical questions about the minimum duration required for oral administration of CM for the patient to obtain clinical benefits, as well as the maximum duration to continue CM after obtaining the benefits. It is worth noting that this study was a retrospective study with incomplete medical records and lower quality of evidence and credibility than prospective randomized controlled studies. Additionally, an immortal time bias may exist in the analysis of duration of the CM administration among the patients in the CM and WM combination group; these issues should be further explored in subsequent prospective clinical studies with larger sample sizes.

Chemoradiotherapy remains the primary option for first-line treatment plans for LS-SCLC. Despite slow research progress, clinical trials have been conducted in multiple aspects of radiotherapy, chemotherapy, immunology, molecular biology, and pathology to maximize patient benefit. Some clinical trials have demonstrated that for LS-SCLC, platinum plus irinotecan may be associated with better OS compared with platinum plus etoposide.[20] With the rise of immunotherapy, studies on SCLC treatment with immunotherapy have been increasing. Studies have also found that some patients may benefit from enhancement of the anticancer activity of T-cells by inhibiting PD1, PDL1, and CTLA4, etc.[29-31] However, the evidence levels of such studies are low, and additional trial data are needed to support these conclusions. Further, the above studies have not impacted the classical EP regimen (etoposide plus cisplatin) as the cornerstone of SCLC treatment, nor have they led to significant OS extension in SCLC patients. Additionally, due to the side effects of immunotherapy and targeted therapy, no significant improvements have been made in the quality of life of SCLC patients. This current study provided new ideas for the comprehensive treatment

of LS-SCLC, as well as the possibility of extending the survival period and improving the quality of life of LS-SCLC patients in the future.

In recent years, preliminary studies on the combination of CM and WM in the treatment of SCLC have been conducted. For example, *Radix Ginseng*, *Poria*, and *Atractylodes macrocephala* powder have been found to reduce the pain and extend the survival of SCLC patients with bone metastases.[32] Animal experiment has verified that the combination of CM using *Java Brucea* fruit oil emulsion with Anlotinib could inhibit the growth and angiogenesis of liver metastases of SCLC.[33] Other clinical studies have shown that CM regimens have improved the 2-, 3-, and 5-year survival rates[34] of LS-SCLC patients after conventional chemoradiotherapy, and that the combination of CM and WM in the treatment of chemotherapy-sensitive SCLC improved patients' survival quality, reduced adverse effects, and tended to extend the OS and PFS.[27]

In conclusion, due to the rapid progression and the high likelihood of recurrence and metastasis with SCLC, the current efficacy of chemoradiotherapy in WM is unsatisfactory, without significant improvement in patient survival under the current treatment model. In addition, due to the traditional concept that CM is slow to take effect, few clinical trials have been conducted on SCLC treatments with integrated CM and WM. However, successful cases of combination treatment of CM and WM for LS-SCLC in clinical practice aroused our interest in its applicability for extending the OS rates for LS-SCLC patients. The current study was a preliminarily exploration, using a combination of historical and real-time follow-up data based on the past treatment and present situation of the study population, to verify the efficacy of integrated CM and WM treatment for LS-SCLC and the potential extension of patients' OS and PFS. Although the sample size was small, this study nevertheless provided clinical guidance and evidence, as well as a plan to guide subsequent clinical studies with larger sample sizes.

Conflict of Interest

None declared.

Author Contributions

Li CH and Hua BJ contributed to study concepts. Qi RZ and He SL contributed to study design. Li Y, Hu JQ, Zhao YW, He J and Cheng MQ contributed to data acquisition. Li CH and Geng L contributed to quality control of data and algorithms. Qi RZ, He SL and Li CH contributed to data analysis and interpretation. Li CH and Hua BJ contributed to statistical analysis. Li CH and Qi RZ contributed to manuscript preparation. Qi RZ, Li Y and Zhao YW contributed to manuscript editing. Li CH contributed to manuscript review. All authors gave the final approval for submission and publicarion of the manuscript.

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