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Original Article

Chinese Medicine Treatment Prolonged Survival in Small Cell Lung Cancer Patients: A Clinical Observation*

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ABSTRACT **Objective:** To evaluate the effect of Chinese medicine (CM) treatment on survival time and quality of life (QOL) in patients with small cell lung cancer (SCLC). **Methods:** This was an exploratory and prospective clinical observation. Patients diagnosed with SCLC receiving CM treatment were included and followed up every 3 months. The primary outcome was overall survival (OS), and the secondary outcomes were progression-free survival (PFS) and QOL. **Results:** A total of 136 patients including 65 limited-stage SCLC (LS-SCLC) patients and 71 extensive-stage SCLC (ES-SCLC) patients were analyzed. The median OS of ES-SCLC patients was 17.27 months, and the median OS of LS-SCLC was 40.07 months. The survival time was 16.27 months for SCLC patients with brain metastasis, 9.83 months for liver metastasis, 13.43 months for bone metastasis, and 18.13 months for lung metastasis. Advanced age, pleural fluid, liver and brain metastasis were risk factors, while longer CM treatment duration was a protective factor. QOL assessment indicated that after 6 months of CM treatment, scores increased in function domains and decreased in symptom domains. **Conclusion:** CM treatment might help prolong OS of SCLC patients. Moreover, CM treatment brought the trend of symptom amelioration and QOL improvement. These results provide preliminary evidence for applying CM in SCLC multi-disciplinary treatment.

KEYWORDS small cell lung cancer, Chinese medicine, survival time, follow-up, quality of life

Lung cancer is in the first place of cancer mortality in Chinese population.[1] Small cell lung cancer (SCLC) counts for 15%–20% in lung cancer, and is considered as a strongly invasive pathological type.[2] The standard treatment for SCLC includes chemotherapy and radiotherapy, while very few patients at early stage could benefit from surgery.[3] Significant progress in targeted therapy and immunotherapy has been made in treating non-small cell lung cancer (NSCLC), but these two therapies have not acquired similar effect in SCLC.[4,5] Initial treatment could bring desirable response, however, about 80% of patients would soon relapse or progress, and the 2nd line treatment is unsatisfactory.[6] Therefore, the therapeutic strategy of SCLC has remained a tough challenge.

The prognosis of SCLC is poor: the 5-year survival rate is lower than 7%, and the average survival time for SCLC is approximately 1 year.[4] Survival time varies distinctively among limited-stage (LS) SCLC and extensive-stage (ES) SCLC. Median survival time (MST) for LS patients is 15–20 months, with a 2-year survival rate at 20%–40%;[7] for patients with ES disease, the MST is 8–13 months and 2-year survival rate is in a level of 5%.[5,7] Progression in radiotherapy including concurrent chemoradiation and prophylactic cranial radiation (PCI) takes effect in response duration prolongation and brain metastasis prevention, though there is no remarkable increase in overall survival (OS) accordingly.[8] Moreover, rise in SCLC survival has been slow over the past decades.[7]

Chinese medicine (CM) treatment has gradually showed efficacy in cancer adjuvant therapy by improving body resistance in perioperative period, reducing side effects of radiotherapy and chemotherapy, as well as preventing relapse and metastasis.[9] Studies showed that CM helped to prolong survival of lung cancer patients,[10,11] but

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few CM studies focused on SCLC. In this study, we followed SCLC patients receiving CM treatment and standard Western medicine (WM) treatment. By observing these patients' survival, we intended to explore the effect of CM on SCLC.

METHODS

Inclusion and Exclusion Criteria

Patients meeting the following criteria were included: (1) confirmed diagnosis of SCLC with imaging and pathological proofs, (2) aged 18–85 years, (3) Karnofsky Performance Status (KPS) score higher than 40, (4) receiving CM treatment for at least 2 months. Patients meeting one or more of the following criteria were excluded: (1) evidence of severe or uncontrolled systemic disease, like cardiac, hepatic, renal or infectious diseases, (2) pregnancy or lactation, (3) receiving immunotherapy or targeted therapy, (4) poor cognitive function, unable to fulfill scale evaluation.

Participants and Study Design

This was an exploratory, single-armed and prospective clinical observation. From July 2015 to June 2018, patients diagnosed with SCLC were recruited with informed consent at the clinic of Oncology Department, Guang'anmen Hospital, China Acadamy of Chinese Medical Sciences. This study was approved by Ethics Committee of Guang'anmen Hospital in accordance with medical ethics standards (Reference: 2017-047-KY). The research complied with the principles of Helsinki Declaration, while study safety was under surveillance of the Ethics Committee.

Participants received WM treatment including chemotherapy, radiotherapy and surgery according to the National Comprehensive Cancer Network (NCCN) clinical guideline of SCLC,[12] and regular CM treatment simultaneously. Demographics and clinical information including age, gender, time of diagnosis and first clinic visit, cancer staging, smoking history, existence of pleural fluid, metastatic spot and WM treatment were carefully recorded.

In order to evaluate the effect of CM treatment, the participants were followed every 3 months. During each follow-up, information including survival situation, results of recent chest and abdomen CT scan, brain MRI scan, bone scintigraphy, complete blood count (CBC) and biochemistry test were collected. Patients were also requested to accomplish a survey to investigate CM intake status as well as quality of life (QOL). In order to improve participants' compliance, research team provided them with outpatient appointment system, and helped establish information communication between participants and team physicians to receive feedback in time. Each patient should be followed for at least 6 months.

CM Therapeutic Scheme

CM treatment mainly relies on syndrome differentiation; however, practitioners' experience and prescriptions varied a lot. Studies indicated that patients receiving chemotherapy and radiotherapy had different CM syndrome,[13,14] which was consistent with our observation. Therefore, to provide better clinical reference, our team set a semi-fixed CM therapeutic plan: the formula was basically determined by WM therapeutic phase and further adjusted according to patient's condition under the guidance of syndrome differentiation.

Patients enrolled in the study were in 3 kinds of status: underwent chemotherapy, underwent radiotherapy and finished WM treatment (including very few patients did not receive WM treatment). As chemotherapy would result in qi deficiency and blood stasis,[13] therapeutic principle of chemotherapy formula was tonifying qi and promoting blood circulation (Appendix 1 formula 1). For those patients who was eligible for surgery, they would soon begin chemotherapy after surgery, and their CM treatment would refer to chemotherapy formula.

Patients underwent radiotherapy would experience cough, expectoration, sore throat and skin ulcers. According to clinical observation and syndrome study,[14] yin deficiency was the main syndrome after radiotherapy. Therefore, nourishing yin and clearing heat was the core CM treatment principle in radiotherapy phase; modified Yangyin Qingfei Decoction (养阴清肺汤) was applied (Appendix 1 formula 2).

For patients completing WM treatment and those did not receive WM treatment, the main pathogenesis was weakened body resistance and excessive toxicity. Therefore, modified Weijing Decoction (苇茎汤) was used during this period to resolve toxicity and reinforce body resistance (Appendix 1 formula 3).

Further adjustment was made according to

patients' symptoms upon syndrome differentiation. Part of the prescription adjustments are listed in Appendix 2. Patients could choose either decoction pieces or dispensing granules that were both provided in the Pharmacy of Guang'anmen Hospital, as clinical effect was reported equivalent between decoction and granule.[15,16] CM should be taken twice a day, and the recommended CM treatment time was 3 years.

Outcome Measurement

The primary outcome was OS, defined as time from diagnosis until death or end of the study. Withdrawn patients were recorded as censored value, and their end point was the last survived follow-up time. The secondary outcomes were progression-free survival (PFS) and QOL. PFS was defined as the time from diagnosis to disease progression or death due to any cause; as censored value was applied to record withdrawn patients. QOL was evaluated by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC-QLQ-C30, EORTC-QLQ-Lung Cancer-Specific (LC13)][17,18] at two follow-up time points with an interval of 6-month CM treatment.

Statistical Analysis

Statistical analysis was performed by SPSS 22.0 for Windows. Quantative statistics were listed as mean ± standard deviations ($\bar{x} \pm s$). Kaplan-Meier method was applied for OS and PFS analysis. Log-rank test was proceeded to explore the prognostic value of different clinical factors, and cox proportional hazard regression model was applied to further confirm the relevance of prognosis. Statistics of QOL received normality test, and further variation analysis was performed by two-sample *t* test or Manne-Whitney test. $P \leqslant 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Totally 136 patients were enrolled in the study, 65 of them were diagnosed as LS-SCLC and 71 were ES-SCLC. Till the last follow-up on January 29, 2019, 9 patients (6.6%) were withdrawn, and their survival data were recorded as censored value. Fourteen patients received surgery, among which 3 received chemoradiotherapy and 9 received chemotherapy alone. In the remaining 122 participants, 71 received chemotherapy and radiotherapy, and 49 received only chemotherapy; 2 patients didn't receive WM treatment. Table 1 shows the detailed information grouped by LS and ES.

Table 1. Demographic and Clinical Characteristics of SCLC Patients (Case)

Index	LS-SCLC (65 cases)	ES-SCLC (71 cases)	Total
Gender			
Male	45	59	104
Female	20	12	32
Smoking history			
Smoker	32	51	83
Non-smoker	33	20	53
Age ($\bar{x} \pm s$, year)	60.94 ± 9.31	62.18 ± 9.81	61.59 ± 9.56
⩾60 years	35	45	80
<60 years	30	26	56
TNM staging			
Ⅰ	11	0	11
Ⅱ	13	0	13
Ⅲ	41	17	58
Ⅵ	0	54	54
Pleural fluid			
Yes	4	18	22
No	61	53	114
Metastasis			
Lung	0	16	16
Liver	0	14	14
Brain	0	14	14
Bone	0	17	17
CM treatment duration			
2–3 months	6	16	22
4–6 months	11	20	31
>6 months	48	35	83

Notes: LS-SCLC, limited-stage small cell lung cancer; ES-SCLC, extensive-stage small cell lung cancer; CM, Chinese medicine; TNM, tumor, necrosis and metastasis. The data of the 3 month was included in the 2-3 month group, the same below

Survival Analysis

The OS of SCLC patients and subgroup analysis are shown in Table 2. Median PFS of ES-SCLC was 13.10 (95% CI 9.58–16.62) months. Median PFS of LS-SCLC and median OS in other subgroups of LS-SCLC patients were not available.

Tables 3 and 4 demonstrate the prognostic value of different characteristics. Log-rank test manifested a statistical difference in age, pleural fluid, liver metastasis, brain metastasis, bone metastasis and CM treatment duration. These variables were further analyzed in cox regression model. The result indicated that advanced age, pleural fluid, liver and brain metastasis were risk factors; CM treatment duration was a protective factor.

Table 2. mOS of Patients with SCLC (Month)

Patient	Case	OS	
		Median	95% CI
ES-SCLC	71	17.27	15.56, 18.97
Chemoradiation		21.27	13.93, 28.60
Chemotherapy		16.50	14.38, 18.62
Without WM		4.17	NA
LS-SCLC	65	40.07	NA
Surgery		38.67	NA
Whole cohort	136	29.30	25.91, 32.69

Notes: SCLC, small cell lung cancer; ES, extensive-stage; LS, limited-stage; CI, confidence interval; OS, overall survival; NA, not available; the same below.

Compared with 2–3 months CM treatment, patients receiving 3–6 months treatment had 0.489 times mortality risk and patients underwent CM treatment longer than 6 months had 0.286 times of mortality risk.

Table 3. Survival Analysis of SCLC Patients Grouped by Clinical Features

Index	mOS/months (95% CI)	Log-rank test
Gender		
Male	27.73 (23.38–32.08)	0.286
Female	30.97 (NA)	
Smoking history		
Smoker	27.00 (18.96–35.05)	0.086
Non-smoker	40.07 (21.42–58.72)	
Age		
<60 years	–	0.001
⩾60 years	22.23 (15.83–28.63)	
Pleural fluid		
Yes	27.00 (10.68–43.32)	0.043
No	30.07 (19.36–40.77)	
Lung metastasis		
Yes	18.13 (0.00–36.63)	0.375
No	29.30 (19.38–39.22)	
Liver metastasis		
Yes	9.83 (6.35–13.32)	0.000
No	30.07 (19.19–40.94)	
Brain metastasis		
Yes	16.27 (12.60–19.93)	0.006
No	30.07 (19.37–40.77)	
Bone metastasis		
Yes	13.43 (7.01–19.86)	0.000
No	30.07 (19.81–40.33)	
CM treatment duration		
2–3 months	14.73 (7.50–21.97)	0.000
3–6 months	22.33 (17.24–27.43)	
>6 months	40.07 (29.44–50.69)	

Notes: SCLC, small cell lung cancer; mOS, median overall survival; CM, Chinese medicine; CI, confidence interval

Table 4. Cox Regression Model of Prognostic Factors in SCLC Patients

Index	*P* value	HR	95% CI
Age (⩾60 years)	0.000	3.114	1.693–5.730
Pleural fluid	0.044	1.957	1.018–3.762
Liver metastasis	0.000	6.646	3.148–14.032
Brain metastasis	0.000	3.795	1.899–7.586
CM treatment duration			
2–3 months			
3–6 months	0.071	0.489	0.225–1.062
>6 months	0.000	0.286	0.147–0.556

Notes: SCLC, small cell lung cancer; HR, hazard ratio; CM, Chinese medicine; CI, confidence interval

Figure 1 shows the survival of 45 subjects with organ metastasis at baseline grouped by metastatic site. The survival time was 16.27 months for patients with brain metastasis, 9.83 months for liver metastasis, 13.43 months for bone metastasis, was 18.13 months for lung metastasis.

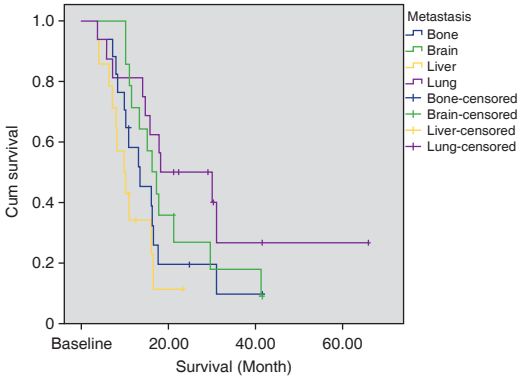

Figure 1. Survival of SCLC Patients with Organ Metastasis at Baseline

Note: SCLC, small cell lung cancer

Evaluation on QOL

The standardized scores of EORTC-QLQ-C30 and EORTC-QLQ-LC13 are shown in Table 5. There was a growing trend in scores of all function domains as well as overall health condition, although no statistical significance was found. However, level of financial burden slightly raised. Scores of various symptoms decreased except for constipation, diarrhea and pain in other parts.

DISCUSSION

Previous studies among Chinese population showed that mOS of LS-SCLC was 23.8–28.5 months[19,20] and mOS of ES-SCLC was 9.13–10.00 months.[21,22] A SCLC cohort conducted in Canada[23] was similar to our study, in which the patients received standardized

Table 5. QOL Assessment in Two Follow-Up Visits of SCLC Patients ($\bar{x} \pm s$, score)

Item	1st follow-up	2nd follow-up	*P*-value
EORTC-QLQ-C30			
Physical functioning	61.59 ± 29.59	65.96 ± 29.09	0.328
Role functioning	57.94 ± 36.52	60.22 ± 34.43	0.821
Cognitive functioning	71.96 ± 26.07	74.67 ± 22.98	0.681
Emotional functioning	58.73 ± 25.20	61.11 ± 27.10	0.368
Social functioning	54.50 ± 32.68	56.67 ± 31.72	0.748
Global health status	50.00 ± 24.23	57.11 ± 23.40	0.109
Financial difficulties	53.97 ± 37.11	52.00 ± 37.66	0.758
Dyspnea	46.56 ± 31.98	40.00 ± 30.51	0.205
Pain	28.31 ± 32.88	24.00 ± 26.60	0.740
Fatigue	54.32 ± 30.34	49.04 ± 27.28	0.364
Insomnia	40.21 ± 38.41	42.22 ± 35.65	0.698
Appetite loss	48.68 ± 35.83	43.56 ± 36.75	0.390
Nausea and vomiting	24.34 ± 28.53	22.67 ± 26.23	0.840
Constipation	28.57 ± 31.03	29.33 ± 28.98	0.753
Diarrhea	17.46 ± 24.58	22.22 ± 29.17	0.426
EORTC-QLQ-LC13			
Coughing	42.33 ± 33.98	32.00 ± 30.23	0.066
Hemoptysis	7.94 ± 21.35	6.22 ± 16.16	0.964
Dyspnea	43.39 ± 31.54	32.59 ± 22.32	0.122
Sore mouth	14.29 ± 27.25	11.11 ± 20.01	0.889
Dysphagia	20.11 ± 31.42	11.11 ± 23.46	0.079
Peripheral neuropathy	22.22 ± 31.68	21.33 ± 27.75	0.859
Alopecia	50.26 ± 38.28	40.44 ± 40.38	0.135
Pain in chest	25.93 ± 32.49	22.22 ± 25.31	0.819
Pain in arms or shoulder	30.69 ± 32.96	25.78 ± 30.30	0.413
Pain in other parts	25.93 ± 32.49	30.22 ± 29.60	0.263

Notes: EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC-QLQ-LC13, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer-Specific; QOL, quality of life

WM treatment and the survival analysis was carefully classified which made it easier for comparison. Results showed that in ES-SCLC, mOS was 9 months with chemotherapy alone and 13 months with the addition of radiotherapy. As for LS-SCLC, mOS of patients receiving surgery combining adjuvant therapy was 40 months and mOS of patients receiving chemoradiation was 32 months. Among ES-SCLC, mOS in our cohort showed at least a 7-month advantage in the chemotherapy group over the Canadian cohort, while LS-SCLC showed no preponderance compared to the surgery group. However, as few SCLC patients could receive surgery and mOS in whole LS-SCLC containing patients who were not eligible for surgery was equivalent to the surgery group in the Canadian cohort, therefore, a 40-month survival in our cohort still had clinical significance. This indicated that SCLC patients receiving CM treatment as adjuvant therapy might have better prognosis than those receiving WM treatment alone. However, by the end of the last follow-up, many LS-SCLC patients didn't reach study endpoint (death), thus some survival statistics of LS-SCLC was not acquired. Further follow-up will be needed to better evaluate LS-SCLC survival.

Through log-rank test and cox regression analysis, we found that age, pleural fluid, liver and brain metastasis, CM treatment duration were prognostic factors. In our study, patients with CM treatment duration longer than 6 months had the best outcome, followed by the 3–6 month group, and 2–3 month group had the shortest survival. To eliminate the impact that patients with short survival were not able to take CM for a long period, we excluded patients with mOS shorter than 6 months and re-performed cox regression analysis; longer CM treatment duration was still a protective factor (3–6 months *vs*. 2–3 months, *P*=0.095, HR=0.504; >6 months *vs*. 2–3 months, *P*=0.002, HR=0.305).

To evaluate the influence of CM treatment on organ metastasis, we applied an Asian cohort[24] as reference. Survival time of liver metastasis in our study was 9.83 months (*vs*. 7.40 months in literature); lung metastasis was 18.13 months (*vs*. 10.03 months); brain metastasis was 16.27 months (*vs*. 13.90 months); bone metastasis was 13.43 months (*vs*. 8.20 months). One sample *t*-test showed significant difference in liver metastasis (*P*=0.041), bone metastasis (*P*=0.007) and lung metastasis (*P*=0.016). Better survival was seen though, however, the sample size was relatively small, thus we might initially speculate that CM helped improve survival of SCLC patients with liver, bone and lung metastasis.

Scale evaluation showed the effect of CM treatment on QOL. Although no statistical significance was found, variation tendency was obvious between two follow-ups. Scores of different function domains and global health status increased, suggesting function improvement. Moreover, scores of symptom domain decreased; coughing, dyspnea, dysphagia and alopecia were relieved in largest degree, indicating CM was effective in treating respiratory symptoms.

There are some limitations in our study. First, this was a single-armed observation, WM treatment group

should be applied in future study to raise evidence grade. Second, as many participants did not reach study endpoint, longer follow-up is needed to acquire precise survival data. Finally, EORTC-QLQ-C30 and EORTC-QLQ-LC13 only provide simple information about change of symptoms; syndrome evolution pattern in combination with symptom variation should be recorded in detail to better illustrate the effect of CM treatment.

In conclusion, our study suggested that CM treatment might help prolong mOS of SCLC patients. Moreover, CM treatment brought the trend of symptom amelioration and QOL improvement. These results provide preliminary evidence for applying CM in SCLC multi-disciplinary treatment.

Conflict of Interest

All authors report no conflict of interest.

Author Contributions

Xu XQ was responsible for study execution and drafting the manuscript; Deng WQ and Li M were responsible for data acquisition; Wang DY conducted data analysis; Kou DL drafted the manuscript; Zhang PT raised the study concept and design, and revised the manuscript. All authors have read and approved the final manuscript.

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