Proceedings of Anticancer Research, 2024, Volume 8, Issue 6
http://ojs.bbwpublisher.com/index.php/PAR
ISSN Online: 2208-3553
ISSN Print: 2208-3545

Real-world Efficacy Analysis of Combined Chinese and Western Medicine in the Treatment of Extensive-stage Small Cell Lung Cancer

Kai Tan[1], Changhui Zhang[1], Puhua Zeng[2,3]*

[1]Hunan University of Chinese Medicine, Changsha 410208, Hunan Province, China
[2]Cancer Research Institute of Hunan Academy of Traditional Chinese Medicine, Changsha 410006, Hunan Province, China
[3]Hunan Academy of Traditional Chinese Medicine Affiliated Hospital, Changsha 410006, Hunan Province, China

***Corresponding author:** Puhua Zeng, zph120@126.com

Abstract: *Objective:* To explore the efficacy of integrated traditional Chinese and Western medicine in the treatment of extensive-stage small cell lung cancer (ES-SCLC). *Methods:* Patients who were hospitalized and outpatients in the Affiliated Hospital of Hunan Academy of Traditional Chinese Medicine from April 1, 2018, to April 1, 2023, were selected and screened according to the inclusion and exclusion criteria. A total of 161 patients were included, of which the control group was chemotherapy combined with traditional Chinese medicine (TCM), and the experimental group was chemotherapy + immunotherapy combined with TCM. The primary endpoint of this study was overall survival (OS), and secondary endpoints included progression-free survival (PFS), objective remission rate (ORR), and disease control rate (DCR). SPSS 25.0 statistical software and R software (version 4.2.1) were used for processing and data analysis. *Results:* The prognosis of patients treated with chemotherapy + immunotherapy combined with TCM was significantly better than that of the chemotherapy combined with TCM group, with median OS (15.07 months vs. 13.3 months, $P = 0.02$) and median PFS (6.87 months vs. 5.97 months, $P = 0.04$). *Conclusion:* Based on adjuvant therapy with TCM, chemotherapy combined with immunotherapy has more advantages than chemotherapy alone in prolonging the median OS and PFS. It can improve the general condition of patients after treatment, enhance their tolerance, and provide basic guarantees for subsequent treatment.

Keywords: Extensive-stage small cell lung cancer (ES-SCLC); Real-world study (RWS); Immunotherapy; Chemotherapy; Traditional Chinese medicine (TCM)

Online publication: November 22, 2024

1. Introduction

Lung cancer is one of the most common malignant cancers worldwide and is the leading cause of cancer-related

deaths [1]. Of those, small cell lung cancer (SCLC) accounts for about 10–20% of all lung cancers [2]. Due to its high degree of malignancy and susceptibility to invasion and metastasis, approximately 2/3 of SCLC patients have developed extensive small cell lung cancer (ES-SCLC) at the time of diagnosis [3]. Treatment options for ES-SCLC are very limited, and platinum in combination with etoposide has been its standard first-line treatment for the past four decades, achieving overall survival (OS) of approximately 10 months in patients with ES-SCLC [4-6]. Although SCLC is highly sensitive to the tumor-killing effects of chemotherapy, chemotherapy has limitations such as toxicity, drug resistance, and tumor heterogeneity [7].

Immune checkpoint inhibitors (ICIs) mainly include programmed cell death 1 (PD-1) and Programmed cell death 1 ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibodies, which aim to reactivate the anti-tumor cytolysis function of T-cells by blocking the inhibitory pathway between T-lymphocytes and tumor cells or antigen-presenting cells [8]. ICIs have dramatically changed the choice of first-line treatment, and there have been many large-scale randomized controlled trials (RCTs) confirming that chemotherapy combined with immunization has shown promising results in improving the prognosis of ES-SCLC patients [9-11]. Traditional Chinese medicine (TCM), as an important part of Chinese tradition, has a long history and rich experience in cancer treatment. Based on the guiding principles of holistic view and evidence-based treatment, TCM uses natural medicines to regulate the balance of yin and yang in the human body, enhance the body's resistance and self-healing, and achieve the purposes of preventing cancer, inhibiting the value-added and invasion of tumor cells, alleviating the toxic side effects of radiotherapy and other medicines, improving the quality of life, and prolonging the survival period [12,13]. With the development of technology and in-depth research, unifying the overall macro-diagnosis that Chinese medicine is good at with the local micro-diagnosis that Western medicine is good at, to form a precise and personalized ES-SCLC treatment plan is a treatment model that meets the characteristics of China's national conditions.

Real-world study (RWS), which is conducted in a real-world setting and involves non-randomized selection of intervention protocols based on the characteristics of the patient's condition and wishes, can provide important information for clinical decision-making, thus transcending the controlled environment of traditional clinical trials [14]. In recent decades, to better establish and improve the clinical efficacy of herbal medicines, they have traditionally been evaluated by RCT [15–17]. However, RCTs have limitations due to the diversity of clinical presentations, complexity of treatment outcomes, and strict inclusion and exclusion criteria [18]. Therefore, it is an open question whether patients in a real-world clinical setting in China would experience the outcomes noted in the RCT study.

This study focuses on the real-world treatment patterns of patients diagnosed with ES-SCLC, including the efficacy of first-line chemotherapy as well as first-line immune-combination chemotherapy treatments under the conditions of TCM treatment, to provide a basis for clinical treatment protocols in different clinical populations.

2. Materials and methods

2.1. Patients

This retrospective study included 161 patients with ES-SCLC who received first-line treatment from April 1, 2018, to April 1, 2023, at the Affiliated Hospital of Hunan Academy of TCM. The last follow-up visit was performed before September 10, 2024. This retrospective study was conducted by reviewing patients' medical records with the approval of the Institutional Ethics Review Committee of Hunan Provincial Institute

of Traditional Chinese Medicine Hospital ([2024] 178). The study protocol was following the Declaration of Helsinki (as revised in 2013). Due to the retrospective nature of this study, the requirement for written informed consent was waived.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients with an Eastern Cooperative Oncology Group Physical Performance Status (ECOG PS) score of 0–2; (2) patients with ES-SCLC diagnosed by histology or cytology; (3) receiving at least 2 courses of antitumor therapy during the treatment period.

Exclusion criteria were as follows: (1) patients receiving non-first-line systemic therapy; (2) patients with significant deficiencies in relevant medical records; (3) patients with comorbidities of other malignant tumors that are being actively treated.

2.3. Data collection

The study divided ES-SCLC patients into two cohorts, chemotherapy + immunotherapy combined with the TCM group as Group 1 and chemotherapy combined with the TCM group as Group 2. Data for each patient were extracted from the medical record, including detailed basic information and clinical characteristics including gender, age, ECOG score, smoking history, family history, site of metastasis (lungs, brain, bone, liver, adrenal glands, pleura, and distant lymph nodes), and treatment regimen.

2.4. Outcome and assessment

The primary endpoint of this study was OS, and secondary endpoints included progression-free survival (PFS), objective remission rate (ORR), and disease control rate (DCR). OS was defined as the time from initial treatment to death from any cause or last follow-up. PFS was defined as the time from initial treatment to the first documentation of disease progression or death. ORR was defined as the proportion of patients whose tumors shrank by a certain amount and remained so for a certain period and encompassed cases in complete remission (CR) and partial remission (PR). The percentage of patients whose tumors have shrunk or stabilized and remained stable for a certain period, encompassing cases of CR, PR, and stable disease (SD). All endpoints were evaluated according to the RECIST guidelines (version 1.1). All patients received active follow-up until September 10, 2024. Follow-up information was obtained by telephone or directly from electronic medical record system files.

2.5. Statistical analysis

All collected data were organized and analyzed using SPSS 25.0 statistical software and R version 4.2.1. Categorical variables were expressed as frequencies and analyzed using the chi-squared test or Fisher's exact test, as appropriate. Univariate Cox proportional hazards regression analysis was performed to evaluate the association between each variable and progression-free survival (PFS) and overall survival (OS). Variables with $P < 0.05$ in the univariate analysis were then included in a multivariate Cox proportional hazards regression model to identify independent prognostic factors. Kaplan-Meier analysis and the log-rank test were used to compare PFS and OS between the two groups. All tests were two-sided with a significance level of $\alpha = 0.05$, and differences were considered statistically significant when $P < 0.05$.

3. Results

3.1. Baseline characteristics

A total of 161 ES-SCLC patients were enrolled, of which 74 selected immunotherapy combined with chemotherapy as first-line treatment (Group 1), and 87 selected etoposide combined with platinum as chemotherapy for anti-tumor treatment (Group 2). The enrolled ES-SCLC patients were mainly male, all had a history of smoking, and the ECOG score was mostly 0–1. There was no significant difference between the two groups in terms of gender, smoking history, chest radiotherapy, metastasis, and family history (**Table 1**).

Table 1. Differences in clinical characteristics between the ES-SCLC patients with chemo-immunotherapy and chemotherapy as first-line

Parameter	Overall (*n* = 161)	Group 1 (*n* = 74)	Group 2 (*n* = 87)	*P*-value
Gender				0.719
Male	142 (88.20%)	66 (89.19%)	76 (87.36%)	
Female	19 (11.80%)	8 (10.81%)	11 (12.64%)	
Age (mean ± SD)	63.71 ± 8.58	63.95 ± 9.09	63.52 ± 8.18	0.753
Radiation therapy				0.948
No	128 (79.50%)	59 (79.73%)	69 (79.31%)	
Yes	33 (20.50%)	15 (20.27%)	18 (20.69%)	
Lung metastases				0.779
No	129 (80.12%)	60 (81.08%)	69 (79.31%)	
Yes	32 (19.88%)	14 (18.92%)	18 (20.69%)	
Brain metastases				0.18
No	117 (72.67%)	50 (67.57%)	67 (77.01%)	
Yes	44 (27.33%)	24 (32.43%)	20 (22.99%)	
Bone metastases				0.612
No	121 (75.16%)	57 (77.03%)	64 (73.56%)	
Yes	40 (24.84%)	17 (22.97%)	23 (26.44%)	
Liver metastases				0.692
No	122 (75.78%)	55 (74.32%)	67 (77.01%)	
Yes	39 (24.22%)	19 (25.68%)	20 (22.99%)	
Adrenal metastases				0.885
No	127 (78.88%)	58 (78.38%)	69 (79.31%)	
Yes	34 (21.12%)	16 (21.62%)	18 (20.69%)	
Pleural metastases				0.683
No	139 (86.34%)	63 (85.14%)	76 (87.36%)	
Yes	22 (13.66%)	11 (14.86%)	11 (12.64%)	
Distant lymph node metastases				0.215
No	128 (79.50%)	62 (83.78%)	66 (75.86%)	
Yes	33 (20.50%)	12 (16.22%)	21 (24.14%)	

Table 2 (Continued)

Parameter	Overall (*n* = 161)	Group 1 (*n* = 74)	Group 2 (*n* = 87)	*P*-value
Other transfers				0.38
No	147 (91.30%)	66 (89.19%)	81 (93.10%)	
Yes	14 (8.70%)	8 (10.81%)	6 (6.90%)	
ECOG				0.839
0–1	116 (72.05%)	55 (67.57%)	61 (57.47%)	
2	45 (27.95%)	19 (25.68%)	26 (29.89%)	
Smoking history				0.646
Non-smoker	73 (45.34%)	35 (47.30%)	38 (43.68%)	
Smoker	88 (54.66%)	39 (52.70%)	49 (56.32%)	
Family history of cancer				0.807
No	147 (91.30%)	68 (91.89%)	79 (90.80%)	
Yes	14 (8.70%)	6 (8.11%)	8 (9.20%)	
Duration of TCM combination therapy < 6 months				0.136
No	82 (50.93%)	44 (59.46%)	38 (43.68%)	
Yes	79 (49.07%)	30 (40.54%)	49 (56.32%)	
Duration of TCM combination therapy 6–12 months				0.369
No	88 (54.66%)	36 (48.65%)	52 (59.77%)	
Yes	73 (45.34%)	38 (51.35%)	35 (40.23%)	
Duration of TCM combination therapy > 12 months				0.439
No	152 (94.41%)	68 (91.89%)	84 (96.55%)	
Yes	9 (5.59%)	6 (8.10%)	3 (3.45%)	

3.2. Evaluation of the efficacy of first-line treatment

The study compared the responses of the two groups at the first assessment. It was found that the ORR and DCR of 74 patients who chose immunotherapy combined with chemotherapy were 43.24% and 85.14%, respectively, and those of 87 patients who chose chemotherapy were 34.48% and 86.21%, respectively, with no significant difference between the two groups (**Table 2**).

Table 2. First-line treatment and response as determined by RECIST v.1.1

Variables	Group 1 (*n* = 74)	Group 2 (*n* = 87)	*P*-value
Response at the first evaluation			
CR	0	0	
PR	32	30	
SD	31	45	
PD	11	12	
ORR (%)	43.24	34.48	0.255
DCR (%)	85.14	86.21	0.846

3.3. Survival analysis

At the end of the follow-up period, 136 patients with ES-SCLC experienced death. 61 patients with ES-SCLC died in Group 1 and 75 in Group 2. In this study, the median PFS for the overall study population was 6.17 months. The median PFS of patients in Group 1 was significantly better than that of Group 2 (6.87 months vs. 5.97 months, $P = 0.04$) (**Figure 1A**). The median OS for the overall study population was 14.3 months. The median OS was significantly better in Group 1 than in Group 2 (15.07 months vs. 13.3 months, $P = 0.02$) (**Figure 1B**).

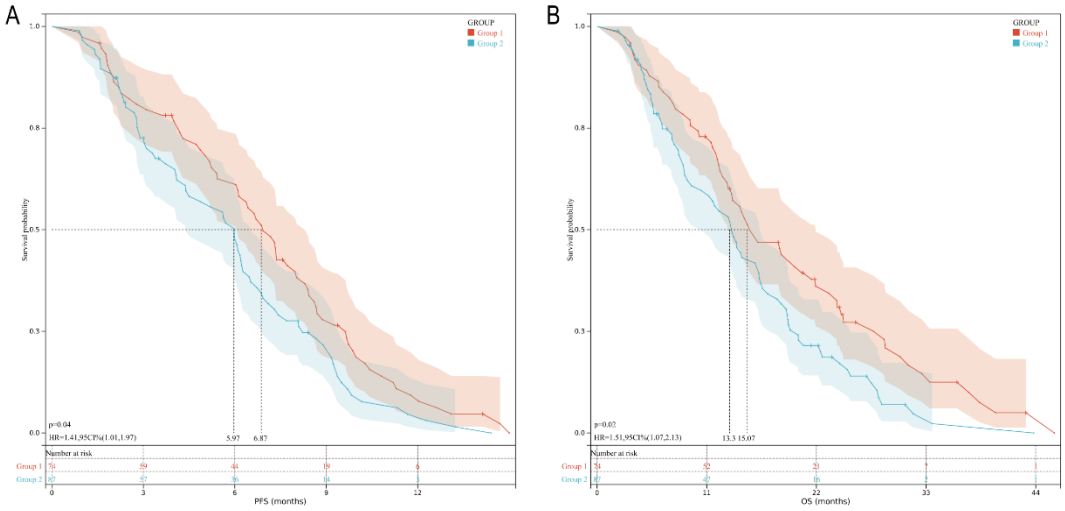

Figure 1. The Kaplan-Meier survival curves of (A) PFS and (B) OS between Group 1 and Group 2.

3.4. Survival risk factors analysis

Potential risk factors for survival were analyzed using univariate and multivariate Cox proportional risk models. Univariate analysis showed that PFS was significantly associated with the factors ECOG, lung radiotherapy, bone metastases, brain metastases, and liver metastases. In multivariate analysis, ECOG, bone metastases, brain metastases, and liver metastases were identified as independent prognostic factors, and all were risk factors (HR > 1) (**Table 3**).

Table 3. Analysis of potential risk factors for PFS using univariate and multivariate Cox proportional hazard models

Characteristics	Univariable analysis HR (95% CI)	*P*-value	Multivariate analysis HR (95% CI)	*P*-value
Gender (male vs. female)	0.799 (0.492–1.297)	0.363		
Age	1.011 (0.991–1.032)	0.276		
ECOG (2 vs. 0–1)	0.328 (0.218–0.494)	< 0.001	3.256 (2.099–5.053)	< 0.001
Smoking history	0.912 (0.654–1.271)	0.586		
Family history of cancer	0.971 (0.544–1.732)	0.921		
Lung radiotherapy	0.642 (0.427–0.964)	0.033	0.840 (0.546–1.293)	0.428
Lung metastases	0.863 (0.563–1.322)	0.499		
Bone metastases	2.456 (1.656–3.643)	< 0.001	2.176 (1.444–3.279)	< 0.001

Characteristics	Univariable analysis HR (95% CI)	*P*-value	Multivariate analysis HR (95% CI)	*P*-value
Brain metastases	2.177 (1.489–3.185)	< 0.001	2.260 (1.529–3.341)	< 0.001
Liver metastases	1.562 (1.059–2.303)	0.025	1.539 (1.027–2.307)	0.037
Adrenal metastases	1.116 (0.741–1.682)	0.598		
Pleura metastases	0.960 (0.603–1.528)	0.863		
Distant lymph node metastasis	1.023 (0.667–1.571)	0.915		
Other metastases	0.817 (0.451–1.479)	0.505		

For OS, univariate analysis was significantly associated with age, ECOG, smoking history, lung radiotherapy, bone metastases, brain metastases, liver metastases, and duration of TCM combination therapy. In multivariate analysis, age, ECOG, smoking history, bone metastases, liver metastases, and duration of TCM combination therapy were identified as independent prognostic factors. Among them, age, ECOG, smoking history, liver metastases, and bone metastases were risk factors (HR > 1), while the duration of TCM combination therapy < 6 months and 6–12 months were protective factors (HR < 1) (**Table 4**).

Table 4. Analysis of potential risk factors for OS using univariate and multivariate Cox proportional hazard models

Characteristics	Univariable analysis HR (95% CI)	*P*-value	Multivariate analysis HR (95% CI)	*P*-value
Gender (male vs. female)	1.442 (0.826–2.519)	0.198		
Age	1.034 (1.013–1.054)	0.001	1.037 (1.014–1.061)	0.001
ECOG (2 vs. 0–1)	3.490 (2.391–5.095)	< 0.001	3.388 (2.192–5.237)	< 0.001
Smoking history	1.475 (1.041–2.091)	0.029	1.963 (1.331–2.896)	0.001
Family history of cancer	1.018 (0.561–1.847)	0.954		
Lung radiotherapy	0.448 (0.290–0.691)	< 0.001	0.660 (0.407–1.070)	0.092
Lung metastases	1.467 (0.956–2.251)	0.079		
Bone metastases	2.428 (1.620–3.640)	< 0.001	2.352 (1.500–3.686)	< 0.001
Brain metastases	1.623 (1.106–2.382)	0.013	1.536 (1.000–2.357)	0.050
Liver metastases	1.544 (1.029–2.316)	0.036	1.567 (1.015–2.420)	0.043
Adrenal metastases	1.326 (0.871–2.017)	0.188		
Pleura metastases	0.944 (0.583–1.527)	0.814		
Distant lymph node metastasis	1.295 (0.829–2.023)	0.257		
Other metastases	0.973 (0.524–1.808)	0.931		
Duration of TCM combination therapy		< 0.001		< 0.001
< 6 months	0.348 (0.242–0.501)	< 0.001	0.416 (0.276–0.629)	< 0.001
6–12months	0.183 (0.085–0.392)	< 0.001	0.214 (0.091–0.505)	< 0.001

4. Discussion

In clinical practice, treatment options for patients with ES-SCLC are limited. The standard first-line treatment for ES-SCLC was platinum-based chemotherapy until immunochemotherapy was approved for clinical use [19]. This study applied the research methodology of a retrospective study to summarize the treatment pattern of ES-SCLC. This study retrospectively included 161 patients with ES-SCLC as a first-line treatment option, and the ratio of patients receiving chemotherapy to chemotherapy combined with immunotherapy was almost 1:1. The results of this study showed that chemotherapy combined with immunotherapy based on herbal adjuvant therapy was more advantageous than chemotherapy alone in prolonging PFS and OS.

The research innovation of this study is the use of retrospective RWS in which 74 patients with ES-SCLC received chemotherapy combined with immunotherapy while 87 patients with ES-SCLC received chemotherapy alone. Ultimately, although there was no significant difference in ORR and DCR values between the two groups, the median PFS and OS of the Chemo-immune group were significantly improved compared with that of the Chemotherapy group, confirming that based on adjuvant therapy with TCM, chemotherapy combined with immunotherapy for ES-SCLC can significantly improve patients' OS and PFS. Paz-Ares *et al.* showed that first-line durvalumab monoclonal antibody plus platinum-etoposide significantly improved OS in patients with ES-SCLC compared to clinically relevant controls, with safety results consistent with the known safety profile of all drugs [20]. Zhang *et al.* found that in terms of OS, serplulimab monoclonal antibody had the greatest OS benefit compared to chemotherapy and that the combination of chemotherapy had the greatest benefit in terms of OS and PFS, and could be the optimal therapy for patients with ES-SCLC [21]. It has been shown that platinum-etoposide chemotherapy plus atilizumab or durvalumab monotherapy reduces the propensity to relapse and the likelihood of adverse events in ES-SCLC [22,23]. It has been shown that thoracic radiotherapy is a feasible treatment for ES-SCLC patients receiving chemoimmunotherapy, and this treatment is particularly suitable for patients without primary liver metastases who receive consolidation therapy with thoracic radiotherapy after chemoimmunotherapy [24,26]. All of these studies suggest that chemotherapy combined with immunotherapy is significantly better than chemotherapy in prolonging OS and PFS in patients with ES-SCLC, which is consistent with the results of this study.

Adjuvant therapy with TCM has been widely used in extensive-stage small-cell lung cancer and has significant advantages in improving patients' quality of life, prolonging patients' survival, and enhancing the tolerance of chemotherapeutic drugs. A study using a multicenter, randomized, single-blind, placebo-controlled clinical trial demonstrated that herbal granules in combination with chemotherapy significantly improved OS in ES-SCLC patients compared with chemotherapy alone [27]. According to evidence-based staging, the median survival of ES-SCLC patients who received Chinese herbal decoction (CHD) for > 3 months was significantly longer than those who received CHD for ≤ 3 months, and the median PPS of patients who received CHD for > 7 months was significantly longer than those who received CHD for < 7 months, while CHD significantly improved physical function [28]. Compared with apatinib alone, "high-exposure herbal medicine" combined with apatinib significantly prolonged PFS when taken for ≥ 6 months in the treatment of patients with ES-SCLC, and "high-exposure herbal medicine" combined with apatinib was significantly effective and relatively safe as maintenance therapy for patients with first- or second-line chemotherapy for ES-SCLC [29,30]. In conclusion, many studies have demonstrated that the use of TCM adjuvant therapy in ES-SCLC patients can significantly increase the patient's tolerance to Western medical treatment and prolong OS and PFS. In this study, the duration of TCM treatment was found to be a protective factor for prognosis in OS multivariate and univariate

analyses, which is consistent with the findings of the above studies. Therefore, adjuvant TCM is an important part of the regimen for patients with ES-SCLC using chemotherapy combined with immunotherapy.

This study also has some limitations: (1) The retrospective collection of clinical data may introduce some bias due to the inherent flaws of retrospective studies. (2) A multicenter large-sample study was not conducted, and the results of the study are subject to some change. Due to these shortcomings, further large phase III prospective studies are needed to validate the findings.

5. Conclusion

Based on adjuvant therapy with TCM, chemotherapy combined with immunotherapy is more advantageous than chemotherapy alone in prolonging PFS and OS, which can improve the general condition of the patients after treatment, improve the tolerance of the patients, and provide a basic guarantee for the follow-up treatment.

Funding

(1) National Natural Science Foundation of China (Project No.: 82074425)
(2) Young Qihuang Scholars Talent Project of National Administration of Traditional Chinese Medicine
(3) Top Technology Leading Talents Project of Hunan Province
(4) Key R&D projects in Hunan Province (Project No.: 2021SK2006)
(5) Natural Science Foundation of Hunan Province (Project No.: 2021JJ30417)
(6) Hunan Provincial Engineering Research Center of Anti-tumor Chinese Medicine Creation Technology Project
(7) Hunan Provincial Health Commission Traditional Chinese Medicine Shennong Leading Talent Project

Disclosure statement

The authors declare no conflict of interest.

References

[1] Sung H, Ferlay J, Siegel RL, et al., 2021, Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians, 71(3): 209–249. https://doi.org/10.3322/caac.21660

[2] Rudin CM, Brambilla E, Faivre-Finn C, et al., 2021, Small-Cell Lung Cancer. Nature Reviews Disease Primers, 7(1): 3. https://doi.org/10.1038/s41572-020-00235-0

[3] Dingemans AC, Früh M, Ardizzoni A, et al., 2021, Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment, and Follow-Up. Annals of Oncology, 32(7): 839–853. https://doi.org/10.1016/j.annonc.2021.03.207

[4] Rossi A, Di Maio M, Chiodini P, et al., 2012, Carboplatin- or Cisplatin-Based Chemotherapy in First-Line Treatment of Small-Cell Lung Cancer: The COCIS Meta-Analysis of Individual Patient Data. Journal of Clinical Oncology, 30(14): 1692–1698. https://doi.org/10.1200/JCO.2011.40.4905

[5] Govindan R, Page N, Morgensztern D, et al., 2006, Changing Epidemiology of Small-Cell Lung Cancer in the United States Over the Last 30 Years: Analysis of the SEER Database. Journal of Clinical Oncology, 24(28): 4539–4544.

https://doi.org/10.1200/JCO.2005.04.4859

[6] Jiang J, Liang X, Zhou X, et al., 2010, A Meta-Analysis of Randomized Controlled Trials Comparing Irinotecan/Platinum with Etoposide/Platinum in Patients with Previously Untreated Extensive-Stage Small-Cell Lung Cancer. Journal of Thoracic Oncology, 5(6): 867–73. https://doi.org/10.1097/jto.0b013e3181d95c87

[7] Korde R, Veluswamy R, Allaire JC, et al., 2022, Small Cell Lung Cancer Patients Treated with Immune Checkpoint Inhibitor: A Systematic Literature Review of Treatment Efficacy, Safety, and Quality of Life. Current Medical Research and Opinion, 38(8): 1361–1368. https://doi.org/10.1080/03007995.2022.2078101

[8] Esposito G, Palumbo G, Carillio G, et al., 2020, Immunotherapy in Small Cell Lung Cancer. Cancers, 12(9): 2522. https://doi.org/10.3390/cancers12092522

[9] Cheng Y, Han L, Wu L, et al., 2022, Effect of First-Line Serplulimab vs Placebo Added to Chemotherapy on Survival in Patients with Extensive-Stage Small Cell Lung Cancer: The ASTRUM-005 Randomized Clinical Trial. JAMA, 328(12): 1223–1232. https://doi.org/10.1001/jama.2022.16464

[10] Wang J, Zhou C, Yao W, et al., 2022, Adebrelimab or Placebo Plus Carboplatin and Etoposide as First-Line Treatment for Extensive-Stage Small-Cell Lung Cancer (CAPSTONE-1): A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. The Lancet Oncology, 23(6): 739–747. https://doi.org/10.1016/S1470-2045(22)00224-8

[11] Goldman JW, Dvorkin M, Chen Y, et al., 2021, Durvalumab, with or without Tremelimumab, Plus Platinum-Etoposide versus Platinum-Etoposide Alone in First-Line Treatment of Extensive-Stage Small-Cell Lung Cancer (CASPIAN): Updated Results from a Randomised, Controlled, Open-Label, Phase 3 Trial. The Lancet Oncology, 22(1): 51–65. https://doi.org/10.1016/S1470-2045(20)30539-8

[12] Wu S, Sun Z, Guo Z, et al., 2023, The Effectiveness of Blood-Activating and Stasis-Transforming Traditional Chinese Medicines (BAST) in Lung Cancer Progression—A Comprehensive Review. Journal of Ethnopharmacology, 314: 116565. https://doi.org/10.1016/j.jep.2023.116565

[13] He Z, Wang Y, Han L, et al., 2023, The Mechanism and Application of Traditional Chinese Medicine Extracts in the Treatment of Lung Cancer and Other Lung-Related Diseases. Frontiers in Pharmacology, 14: 1330518. https://doi.org/10.3389/fphar.2023.1330518

[14] Pasello G, Pavan A, Attili I, et al., 2020, Real World Data in the Era of Immune Checkpoint Inhibitors (ICIs): Increasing Evidence and Future Applications in Lung Cancer. Cancer Treatment Reviews, 87: 102031. https://doi.org/10.1016/j.ctrv.2020.102031

[15] Wang XQ, Zhang Y, Hou W, et al., 2019, Association Between Chinese Medicine Therapy and Survival Outcomes in Postoperative Patients with NSCLC: A Multicenter, Prospective, Cohort Study. Chinese Journal of Integrative Medicine, 25(11): 812–819. https://doi.org/10.1007/s11655-019-3168-6

[16] Xiao Z, Chen Z, Han R, et al., 2021, Comprehensive TCM Treatments Combined with Chemotherapy for Advanced Non-Small Cell Lung Cancer: A Randomized, Controlled Trial. Medicine, 100(18): e25690. https://doi.org/10.1097/MD.0000000000025690

[17] Li CL, Hsia TC, Yang ST, et al., 2022, Efficacy of Prophylactic Traditional Chinese Medicine on Skin Toxicity of Afatinib in EGFR Mutation-Positive Advanced Lung Adenocarcinoma: A Single-Center, Prospective, Double-Blinded, Randomized-Controlled Pilot Trial. Integrative Cancer Therapies, 21: 15347354221086663. https://doi.org/10.1177/15347354221086663

[18] Di Maio M, Perrone F, Conte P, 2020, Real-World Evidence in Oncology: Opportunities and Limitations. The Oncologist, 25(5): e746–e752. https://doi.org/10.1634/theoncologist.2019-0647

[19] Yu Y, Chen K, Fan Y, 2023, Extensive-Stage Small-Cell Lung Cancer: Current Management and Future Directions.

International Journal of Cancer, 152(11): 2243–2256. https://doi.org/10.1002/ijc.34346

[20] Paz-Ares L, Dvorkin M, Chen Y, et al., 2019, Durvalumab Plus Platinum-Etoposide versus Platinum-Etoposide in First-Line Treatment of Extensive-Stage Small-Cell Lung Cancer (CASPIAN): A Randomised, Controlled, Open-Label, Phase 3 Trial. Lancet, 394(10212): 1929–1939. https://doi.org/10.1016/S0140-6736(19)32222-6

[21] Zhang T, Li W, Diwu D, et al., 2023, Efficacy and Safety of First-Line Immunotherapy Plus Chemotherapy in Treating Patients with Extensive-Stage Small Cell Lung Cancer: A Bayesian Network Meta-Analysis. Frontiers in Immunology, 14: 1197044. https://doi.org/10.3389/fimmu.2023.1197044

[22] Falchero L, Guisier F, Darrason M, et al., 2023, Long-Term Effectiveness and Treatment Sequences in Patients with Extensive-Stage Small Cell Lung Cancer Receiving Atezolizumab Plus Chemotherapy: Results of the IFCT-1905 CLINATEZO Real-World Study. Lung Cancer, 185: 107379. https://doi.org/10.1016/j.lungcan.2023.107379

[23] Wang T, Li Y, Zheng X, 2023, Cost-Effectiveness of the Combination of Immunotherapy and Chemotherapy for Extensive-Stage Small-Cell Lung Cancer: A Systematic Review. BMC Health Services Research, 23(1): 691. https://doi.org/10.1186/s12913-023-09727-7

[24] Cai Z, Gu X, Xie J, et al., 2023, Safety and Efficacy of Thoracic Radiotherapy Combined with Chemo-Immunotherapy in Patients with Extensive-Stage Small Cell Lung Cancer: A Multicenter Retrospective Analysis. Translational Lung Cancer Research, 12(10): 1987–2000. https://doi.org/10.21037/tlcr-23-294

[25] Konala VM, Madhira BR, Ashraf S, et al., 2020, Use of Immunotherapy in Extensive-Stage Small Cell Lung Cancer. Oncology, 98(11): 749–754. https://doi.org/10.1159/000508516

[26] Valette CA, Filleron T, Debieuvre D, et al., 2023, Treatment Patterns and Clinical Outcomes of Extensive-Stage Small Cell Lung Cancer (SCLC) in the Real-World Evidence ESME Cohort Before the Era of Immunotherapy. Respiratory Medicine and Research, 84: 101012. https://doi.org/10.1016/j.resmer.2023.101012

[27] Chen Y, Yu M, Liu Z, et al., 2021, Effects of Traditional Chinese Medicine Combined with Chemotherapy for Extensive-Stage Small-Cell Lung Cancer Patients on Improving Oncologic Survival: Study Protocol of a Multicenter, Randomized, Single-Blind, Placebo-Controlled Trial. Trials, 22(1): 437. https://doi.org/10.1186/s13063-021-05407-1

[28] Liu R, He SL, Zhao YC, et al., 2015, Chinese Herbal Decoction Based on Syndrome Differentiation as Maintenance Therapy in Patients with Extensive-Stage Small-Cell Lung Cancer: An Exploratory and Small Prospective Cohort Study. Evidence-Based Complementary and Alternative Medicine, 2015: 601067. https://doi.org/10.1155/2015/601067

[29] Wang M, Jiang H, Zhang M, et al., 2021, "Highly Exposed Chinese Herbal Medicine" Combined with Apatinib as Maintenance Treatment Following First-Line or Second-Line Chemotherapy for Extensive-Stage Small-Cell Lung Cancer: A Single-Arm, Prospective Study. Dose-Response, 19(4): 15593258211055016. https://doi.org/10.1177/15593258211055016

[30] Leem J, 2015, Is Traditional Chinese Herbal Medicine Effective in Prolonging Survival Times in Extensive-Stage Small-Cell Lung Cancer Patients? Integrative Medicine Research, 4(4): 256–9. https://doi.org/10.1016/j.imr.2015.09.004