Progress in diagnosis and treatment of small cell lung cancer with integrated traditional Chinese and Western medicine

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Competing interests
The authors declare no conflicts of interest.

Abbreviations
SCLC, Small cell lung cancer; NSCLC, Non-small cell lung cancer; TCM, Traditional Chinese medicine; LS-SCLC, Limited-stage; ES-SCLC, Extensive-stage; CHM, Chinese herbal medicines; OS, Overall survival; EP regimen, Etoposide and Cisplatin; CPM, Chinese patent medicines; IL, Interleukin; VEGF, Vascular Endothelial Growth Factor; PFS, Progression-free survival; FDA, Food and Drug Administration; PD-L1, Programmed cell death ligand 1; PD-1, Programmed cell death 1; TMB, Tumor mutation burden.

Peer review information
TMR Integrative Medicine thanks Yu-Feng Zhang and other anonymous reviewers for their contribution to the peer review of this paper.

Citation

Executive editor: Guang-Ze Ma.
Received: 19 February 2022; Accepted: 20 March 2022;
Available online: 23 March 2022.
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Abstract
Lung cancer is one of the most common major diseases that seriously threaten human health, lung cancer includes small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Although patients with SCLC account for about 20% of the total number of patients with lung cancer, the mortality rate is much higher than that of patients with NSCLC. Integrated traditional Chinese and Western medicine has obvious advantages in the treatment of patients with SCLC. According to the relevant literature reports on the treatment of SCLC in recent years, this article will summarize the research progress of integrated traditional Chinese and western medicine in the treatment of SCLC from the aspects of traditional Chinese medicine (TCM) combined with surgery, chemotherapy, radiotherapy, and molecular targeted therapy.

Keywords: small cell lung cancer (SCLC); integrated traditional Chinese and Western medicine; progress in diagnosis and treatment
Background

Primary bronchial lung cancer, referred to as lung cancer, is a malignant tumor originating from the bronchial mucosa or glands of the lung, and its morbidity and mortality are at the forefront of malignant tumors at home and abroad. Over the years, the morbidity and mortality of lung cancer have gradually increased, hindering the increase of life expectancy in countries around the world. SCLC accounts for more than 20% of lung cancer and is prone to metastasis at an early stage. The average survival time of Extensive stage small cell lung cancer patients without treatment is only 6–8 weeks, with the strong invasion of cancer cells and extremely poor condition of patients [1]. In recent years, the survival rate of patients with NSCLC has improved rapidly, but the survival rate of patients with SCLC remains at 14% to 15%, less than 50% of the survival rate of patients with non-SCLC [2]. The modern western medicine treatment of lung cancer is mainly surgery, chemotherapy, radiotherapy, molecular targeted therapy, and immunotherapy, in which the effective rate of molecular targeted therapy has been significantly improved in recent years, however, drug resistance and side effects caused by various treatment methods have seriously affected the quality of life of patients, western medicine is still lack of appropriate drugs and interventions [3]. Radiotherapy and chemotherapy are still the standard treatment for Limited-stage (LS-SCLC) and extensive-stage (ES-SCLC) in the diagnosis and treatment of SCLC in western medicine. However, recurrence and metastasis are easy to occur after standard treatment, drug resistance to chemotherapy and high recurrence and metastasis rate after standard treatment are still difficult medical problems in clinical practice. Reducing the recurrence and metastasis of SCLC after standard treatment and prolonging the survival time of patients is the focus of prevention and treatment of SCLC [4]. After long-term clinical and experimental research, it is found that TCM is not only effective in the treatment of lung cancer but also has more obvious advantages in reducing the adverse reactions produced by western medicine and prolonging the survival time of patients. Therefore, the treatment of lung cancer has gradually developed to the direction of integrated traditional Chinese and Western medicine [5, 6]. In this paper, the treatment of SCLC with integrated traditional Chinese and western medicine in recent years is summarized as follows.

Syndrome differentiation and treatment of SCLC in TCM

There is no “lung cancer” name in traditional medicine, according to the symptoms and signs, it belongs to the categories of “pulmonary accumulation” and “Xiben” in TCM. As the Nanjing said, “The accumulation of the lungs, called Xibi, is as big as a cup under the right flank. It lasts for a long time, making people feel cold and hot, wheezing and coughing, and causing congestion of the lungs.” “Plain Questions - Treatise on Strange Diseases,” said, “under the threat of disease, full of Qi and upward reversal,….. The name of the disease is Xiji, which doesn't interfere with diet.” As for the treatment of lung cancer, the ancient records of TCM records have experienced the perfection from the application of simple drugs in the Pre-Qin Dynasty to the application of principle-method-recipe-medicines in the Ming and Qing Dynasty [7]. In the long-term clinical practice, modern TCM experts have summarized the unique ideas and experience of syndrome differentiation and treatment of lung cancer, which has important guiding significance for the research and application of integrated traditional Chinese and Western medicine therapy for lung cancer [6]. Like most malignant tumors, the death of lung cancer is more often caused by multiple organ injuries, failure, and excessive consumption of systemic substances and energy, rather than the primary focus itself [8]. Clinical practice has found that phlegm and blood stasis are important etiology and pathogenesis in the occurrence and development of lung cancer. Phlegm toxin and blood stasis toxin gather in the human body and finally form lung cancer [9]. Compared with NSCLC, SCLC patients have more phlegm toxin and blood stasis toxin, and in the early stage of the disease, phlegm toxin and blood stasis toxin in SCLC patients have spread to other organs of the body, resulting in multiple organs being invaded by the evil toxin, causing serious damage to vital qi and causing serious damage to the body.

Professor Hua Baojin believes that the pathogenesis of SCLC is based on positive deficiency, smoke poison invasion, loss of qi rising, and fall. Smoking is the main risk factor of SCLC, smoke poisons the lung consumes lung yin due to dryness, and damages blood vessels with poison. “Plain Question Another Discussion on Meridians,” said, “the airflow of the meridians, the meridians belong to the lung, the lung collects all meridians”, lungs are delicate organs susceptible to evil influence, the lung qi is damaged, and then the smoke and poison flow through the whole body with the blood, which will inevitably lead to the dysfunction of the viscera. The spleen is damaged and then the lung is injured, the spleen loses function and produces phlegm and dampness, which stops accumulating in the lungs. Although SCLC is common with lung symptoms such as cough, shortness of breath, chest pain, hemoptysis, and other lung symptoms, it reflects the deficiency of vital qi in the body, which is not enough to drive out evil spirits, the rise, and fall of visceral Qi machine is an imbalance, and the disease and evil stop in the lung to form cancer. It is mentioned in Plain Questions Comment on Febrile Diseases “Where evil gathers together, its qi must be deficient.” With the joint efforts of modern doctors’ practical experience and clinical basic research, it is proposed that “positive deficiency” is the root cause of the occurrence and progression of SCLC (Table 1) [10]. SCLC has rapidly progress and strong invasiveness. It is sensitive to first-line chemotherapeutic drugs such as etoposide, platinum injection, and radiation. Professor Hua Baojin focuses on “supplementing qi and strengthening health, supplement led by expelling evil and detoxification”. The treatment of SCLC will be carried out by strengthening the vital energy and regulating the rise and fall of qi throughout the treatment of SCLC.

Zhou Dailan and Lin Lixiu believe that the pathogenesis of lung cancer is not separated from the lung and spleen, because the lung and spleen and are closely related to the generation of qi and body fluid metabolism [12, 13]. The spleen transports and transforms the essence of water and grain, the lungs breathe and inhale natural clear qi, and the second gasification accumulates in the chest, passing through the rest channel, breathing, passing through the heart pulse, and promoting qi and blood. The spleen is the source of phlegm, and the lung is the device for storing phlegm. The movement and transformation of spleen deficiency are unbalanced, water dampness stops inside, dampness accumulates to generate phlegm, phlegm forms strong invasion, the lung qi is damaged, the spleen loses function and produces phlegm and blood stasis closely related to the generation of qi and body fluid metabolism [12, 13]. The spleen transports and transforms the essence of water and grain, the lungs breathe and inhale natural clear qi, and the second gasification accumulates in the chest, passing through the rest channel, breathing, passing through the heart pulse, and promoting qi and blood. The spleen is the source of phlegm, and the lung is the device for storing phlegm. The movement and transformation of spleen deficiency are unbalanced, water dampness stops inside, dampness accumulates to generate phlegm, phlegm forms strong invasion, the lung qi is damaged, the spleen loses function and produces phlegm and blood stasis closely related to the generation of qi and body fluid metabolism [12, 13].

Gao Yang grasped the core pathogenesis of lung cancer and formulated the method of tonifying the lung and dispersing knots. The prescription was added or subtracted by Chen Xia Liujunzi decoction, Yiqi Chatan decoction, Jinfu'an decoction, and so on. According to the symptoms of patients at each follow-up visit, the focus of lung qi deficiency, spleen deficiency, lung yin deficiency, and kidney essence loss is judged. The methods of "benefiting the lung" such as tonifying the lung and spleen, nourishing yin and moistening the lung, and tonifying the lung and kidney are often used. Cooked Tangshans, Astragalus membranaceus, five finger peach, Poria cocos, Atractylodes macrocephala, lily, mountain conch, Ophiopogon japonicas, loquat leaf, Cornus Officinails, yam, Ligustrum lucidum, Eclipta, and other drugs are selected. According to the dynamic changes of phlegm-dampness blocking the lung, accumulation of phlegm-heat in the lung, lung qi stagnation and blood stasis block, the methods of dispelling phlegm, clearing lung and resolving phlegm, regulating lung and removing blood stasis, and so on are commonly used in Pinellia ternata, Fritillaria thunbergii, cat's claw ginger, and houttuynia cordata, loquat leaves, almonds, Platycodon grandiflorum, Fructus Aurantii, Panax notoginseng, Pleurotus ostreatus, gecko, submitting a manuscript: https://www.tmrjournals.com/im
peach kernel, centipede and other drugs [15].

**Treatment of SCLC with integrated traditional Chinese and Western Medicine**

**TCM combined with surgery**

For patients with SCLC, because some micrometastases in the body are not completely controlled before the operation, the operation is a blow to the patients, resulting in a decline in immunity, which may lead to metastasis. Therefore, surgical treatment is an unconventional recommended treatment, for limited-time patients, indications should be strictly selected. Patients with stage IA and IB are the first choice for surgery, and pulmonary lobectomy with mediastinal lymph node dissection is the first choice. Patients with stage IIA and IIB can also consider surgery, while patients with stage III usually do not choose surgery [16]. Although surgical treatment is not routinely recommended, based on data from the United States, it is believed that surgery for stage I and II SCLC can significantly benefit [17]. TCM has gradually shown its effectiveness in tumor adjuvant therapy by improving perioperative body resistance, reducing side effects of radiotherapy and chemotherapy, and preventing recurrence and metastasis [18, 19]. After surgical treatment, the skin, muscles, and bones of the body are damaged, and the vital qi of the body is inevitably damaged. *Huangdi Neijing* “The good qi is kept inside, and evil cannot be done.” Only when upright qi is filled, can the body have enough ability to fight disease and evil. If the body is deficient in vital qi, it is easy to be invaded by disease and evil. SCLC patients lack vital qi, if attacked by disease, the body is not enough to resist disease, easy to be attacked by disease, which is not conducive to the rehabilitation of patients. Therefore, the postoperative treatment of SCLC patients combined with TMR has a good effect on invigorating the spleen and replenishing qi. The spleen can slightly absorb and transfer the essence of water grain replenishing qi. The spleen can slightly absorb and transfer the essence of water grain replenishing qi. The spleen can slightly absorb and transfer the essence of water grain replenishing qi. The spleen can slightly absorb and transfer the essence of water grain replenishing qi. The spleen can slightly absorb and transfer the essence of water grain replenishing qi. The spleen can slightly absorb and transfer the essence of water grain replenishing qi. The spleen can slightly absorb and transfer the essence of water grain replenishing qi. The spleen can slightly absorb and transfer the essence of water grain replenishing qi. The spleen can slightly absorb and transfer the essence of water grain replenishing qi. The spleen can slightly absorb and transfer the essence of water grain replenishing qi. The spleen can slightly absorb and transfer the essence of water grain replenishing qi. 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Zhao Yuwei and others have shown that strengthening the spleen and stomach and nourishing vital energy after the operation is very beneficial to improve the survival rate of patients with SCLC [20]. Jianping Yiqi recipe is composed of Codonopsis pilosula, Large-headed atractylodes, Poria cocos, Honey-fried licorice root, Ginger processed pinellia, Dried orange peel, Parched Hawthorn fruit, Coke malt, Charred triplet, Endothelium corneum Nigeria Galli, Amomum villosum, and Semen coicis. This recipe treats codonopsis pilosula as the monarch drug in a prescription, which plays the role of tonifying the spleen and replenishing qi. Some modern pharmacological studies have found that Codonopsis pilosula can regulate gastric contraction and regulate the release of inflammatory factors to protect gastrointestinal mucosa. Moreover, Codonopsis pilosula polysaccharides can also enhance the phagocytosis of the reticuloendothelial system and exert immunomodulatory function [21]. Some studies have also found that Codonopsis pilosula can improve the tissue structure of alveolar cells, reduce the production of inflammatory factors, and then improve lung function and make lung qi rise and decrease normally [22]. In this prescription Large-headed atractylodes, Poria cocos, Semen coicis, and Dried orange peel are combined, benefiting water and dampness, invigorating the spleen and replenishing qi, tonify the lungs, and having a direct therapeutic effect on the accumulation of dampness in the body and the growth of phlegm in the body caused by deficiency of lung and spleen qi, is a ministerial drug. Ginger processed pinellia, Charred triplet, and Endothelium corneum Nigeria Galli can give full play to the effect of relieving qi and digesting food and has a good control effect on patients who are fatigued, sluggish, and bloating. And they are adjuvants in the prescription. Amomum can clear the movement of vital energy and dispel dampness. Licorice is sweet, reconciling all kinds of medicine, acting together as a causative medicine. Multiple medicines work together to strengthen the spleen and invigorate the lungs, effectively alleviating cancer-triggered persistent fatigue [23].

**TCM combined with chemotherapy**

In the process of radiotherapy, chemotherapeutic drugs have the characteristics of “heat and poison”. At this stage, professor Hua Baojin takes invigoration the spleen and stomach and nourishing the liver and kidney as the basic treatment, “warming the spleen and stomach, invigorating the dryness”, invigorating the spleen and stomach to replenish qi and fluid, tonifying the liver and kidney to nourish blood and nourishing yin, reconciling qi, blood, yin, and yang, and elevating qi [4, 10, 11, 20]. It has been proved that Professor Hua Baojin’s method of connecting the diagnosis and treatment of TMR with western medicine can significantly improve the survival rate of SCLC patients [24]. Combinatorial therapy, using Lion’s mane and Astragalus, Elixao paste during chemotherapy can reduce the incidence of myelosuppression, and the Xuefuzhuyu capsule can improve the hypercoagulable state of blood and improve the effect of chemotherapy [25].

Patients with SCLC are usually treated with chemotherapy after operation. Yu-Hui and others conducted a Meta-analysis on the efficacy of TCM combined with chemotherapy in the treatment of ES-SCLC and discussed its clinical efficacy and safety [26]. Compared with chemotherapy alone, TCM combined with chemotherapy can improve the objective remission rate of treatment (RR = 1.29, 95%CI (1.10, 1.52), P = 0.002). Duan Jincheng conducted a randomized controlled study on 58 patients with SCLC treated with TCM combined with chemotherapy and 38 patients with SCLC treated with chemotherapy alone, the results showed that the combination of the two could strengthen the effect of detoxification and anticancer and improve the effective rate of chemotherapy (P < 0.05) [27]. Zhang Wei and others found that chemotherapy combined with TCM for promoting blood circulation and removing blood stasis showed that the 1-year, 2-year and 3-year survival rates of the experimental group were higher than those of the control group, and there was a significant difference of [28]. Hu Jiaqi and others have shown that Shenqi Fuwzheng injection combined with conventional chemotherapy can increase the objective remission rate and disease control rate of patients with SCLC by about 11% and 6%, respectively, compared with chemotherapy alone. Meta-analysis showed that Shenqi Fuwzheng injection combined with routine chemotherapy could improve the objective remission rate of patients with SCLC (RR = 1.19, 95%CI (1.06, 1.33), P = 0.003) and disease control rate (RR = 1.08, 95%CI (1.02, 1.14), P = 0.01) [29]. From the above evidence, TCM combined with chemotherapy can effectively improve the efficacy of chemotherapy in ES-SCLC patients. After the end of the chemotherapy process, Professor Hua Baojin believes that recuperating the spleen and stomach is to protect the vital qi, to make the spleen and stomach move healthily, to transport the vital qi to the lungs, to grow the lung qi, to smooth the way for the human body to discharge water, to maintain the liver and kidney, to strengthen the bones, and to nourish the blood veins. Phlegm and dampness have no way to gather. Spleen qi rising and clearing, lung qi decreasing, qi rising and falling returning to normal, promoting blood circulation and removing blood stasis, clearing heat and detoxification, and clearing lung meridians. Therefore, tonifying qi, invigorating spleen, activating blood circulation and detoxification as the basic treatment, clearing heat, promoting blood circulation, and removing blood stasis in the lung meridian based on strengthening the body can effectively prolong the survival
time of patients with SCLC [4, 10, 11, 20]. Dong Haitao’s research also shows that radiotherapy and chemotherapy combined with TCM can benefit patients in long-term survival. Proprietary Chinese medicine and TCM preparations are also used in the treatment of SCLC [30].

Clinical observation has provided several cases of Chinese herbal medicines (CHM) prolongation of OS-ES-SCLC patients with overall survival (OS) to improve the survival rate. For example, compared with radiotherapy alone and post-chemotherapy, the median overall survival rates of patients treated with TCM were 7.6 months and 11.1 months, respectively, and the 1-year survival rates were 18.2% and 38.6%, respectively [31]. Zhang Niuhei et al randomly divided 78 cases of SCLC into treatment groups with TCM combined with chemotherapy and the control group with chemotherapy alone. There were 36 patients in each group. The survival rates of 11 months, 22 months, and 33 months in the two groups were compared with those in the control group. Survival benefit (P < 0.05) [32]. From the above evidence, it can be concluded that TCM combined with chemotherapy can effectively prolong the survival time of SCLC patients.

A large number of studies have shown that chemotherapy can effectively kill tumor cells and control tumor growth, recurrence, and metastasis, but at the same time, the damage of normal cells caused by chemotherapy cannot be ignored, the adverse reactions include decreased immune function, myelosuppression, gastrointestinal reactions, myocardial cells, liver, and kidney function damage and so on. TCM plays a significant role in the treatment of adverse reactions caused by chemotherapy, chemotherapy combined with TCM, and other TCM treatments can effectively control the development of tumors and improve patients’ immunity and bone marrow hematopoietic function. Improve gastrointestinal discomfort and protect the heart, liver, kidney, and other organs to ensure the quality of life of patients [33]. SCLC doubles rapidly and is extremely sensitive to chemotherapy, and once found, chemotherapy is usually the first choice. During chemotherapy in patients with SCLC combined with Xuefu Zhuyu decoction can significantly improve the level of pulmonary function and improve TCM syndrome in patients with the syndrome of blood stasis blocking lung collaterals. If tonifying qi and nourishing yin, invigorating spleen and kidney combined with heat-clearing and detoxification, resolving phlegm and anti-cancer can reduce gastrointestinal reaction and improve quality of life [34]. Lao Li et al showed that Yanghe decoction combined with Etoposide and Cisplatin (EP regimen) in the treatment of ES-SCLC patients with Yang deficiency and cold coagulation, can relieve patients’ discomfort such as cough, expectoration, shortness of breath, and fatigue, improve their quality of life, and reduce the incidence and severity of myelosuppression, liver, and kidney function damage after chemotherapy [35]. Therefore, Yanghe decoction combined with chemotherapy in the treatment of ES-SCLC not only has high safety but also has a better clinical effect than that of the simple chemotherapy group.

In the clinical practice of treating SCLC with classical prescriptions, Professor Hua Baojin followed the ancient treatment principles without being bound by them, gave full play to the distinctive characteristics of classical prescriptions, and combined, added, and subtracted different classical prescriptions according to the complexity of the pathogenesis of SCLC. For example, during chemotherapy, nausea, vomiting, and abdominal distention are seen, and more serious conditions are vertigo and fatigue, which belong to the syndrome of Liver Qi stagnation and spleen qi deficiency, liver qi stagnation and phlegm, and blood stasis in the later stage of maintenance and consolidation treatment of SCLC patients after radiotherapy. The treatment principle is to support righteousness and eliminate evil, and the treatment method is to benefit lung and disperse nodules. In this process, the western medicine treatment of the patients is carried out by the SCLC clinical guidelines, which can delay the recurrence and metastasis of SCLC and make it possible for the patients to survive for a long time [15, 45].

Patients who receive radiation can develop dry mouth, dysphagia, skin ulcers, and some trials focusing on CPM have been conducted, including when-qi-fu-zheng injection, compound Radix Sophorae flavescence injection, and ai-shi injection [42]. From the above evidence, it can be concluded that TCM combined with chemotherapy can reduce the response to chemotherapy and improve the quality of life of patients.

TCM combined with radiotherapy
Concurrent radiotherapy and chemotherapy is the standard mode of treatment for patients with LS-SCLC, as for the choice of the timing of radiotherapy, foreign studies have shown that the earlier the simultaneous radiotherapy, the longer the progression-free survival, the median survival and the overall survival, which indicates that the benefit of early radiotherapy is greater [43]. In the course of treatment, Wang Huiming on 67 cases of small cell undifferentiated lung cancer patients with oral etoposide 3 courses, bronchial artery perfusion chemotherapy 3~6 times, radiotherapy 2~3 courses of treatment, and treated with TCM syndrome differentiation and rehabilitation. Each case was followed up for 6~12 months to evaluate its curative effect and adverse reactions, the results showed that among the 67 patients, 21 cases were in complete remission, 36 cases were stable, 10 cases died within 12 months, and the survival rate within 12 months was 85% [44]. Compared with the patients treated with radiotherapy alone, the survival rate of patients treated with TMR combined with radiotherapy is higher.

From the point of view of TCM, radiation has the same nature of “heat and poison” as chemical drugs. Therefore, Chen Hongyu, Wang Wenzhong, Cao Yang, and others have always grasped the core pathogenesis of lung and spleen qi deficiency, lung qi stagnation and phlegm, and blood stasis in the later stage of maintenance and consolidation treatment of SCLC patients after radiotherapy. The treatment principle is to support righteousness and eliminate evil, and the treatment method is to benefit lung and disperse nodules. In this process, the western medicine treatment of the patients is carried out by the SCLC clinical guidelines, which can delay the recurrence and metastasis of SCLC and make it possible for the patients to survive for a long time [15, 45].

Patients who receive radiation can develop dry coughing, expectoration, sore throat, and skin ulcers. According to clinical observation and syndrome study, the main syndrome after radiotherapy is yin deficiency, and the differentiation is lack of kidney yang. If the disease belongs to Shaolin, add Sini decoction or Shengqi Pill to warm and tonify kidney yang and help Yang turn Qi. In case of belching swallowing acid, fear of cold, epigastic fullness, chills in hands and feet, and mixed chills and heat, the prescription of Wumei Pill should be added to warm the liver pulse and clear the upper and lower temperature, which can effectively alleviate the adverse reactions of chemotherapy [4]. Zhuang Ying used Linggu Zhanqun Decoction to observe 32 patients with SCLC undergoing chemotherapy. It was found that the total inhibition rate of vomiting in patients treated with TMR after chemotherapy could reach 93.75% [36].

The application of TCM Kangfuxin liquid, Shenqi Fuzheng injection, Kangai injection, Compound Sophora flavescence, and so on injection during chemotherapy can prevent the decrease of leukocyte and gastrointestinal reaction caused by chemotherapy, and improve the tolerance of patients to chemotherapy drugs. Brucea javanica oil emulsion injection is also safe and effective during brain radiotherapy [25, 37]. In addition, chemotherapy-related nausea and vomiting in patients with SCLC can be relieved by western medicine combined with acupuncture. And myelosuppression can be improved by moxibustion at Zusanli point. Moreover, the daily practice of Baduanjin can also improve the quality of life of SCLC chemotherapy patients [38~40]. The Meta-analysis conducted by Yu-Hui et al shows that TMR combined with chemotherapy can improve the quality of life of patients (RR = 3.41, 95%CI (1.45, 6.80), P = 0.004) [25]. In addition, CHM in conjunction with chemotherapy demonstrated significant improvements in quality of life and a reduction in anemia and neutropenia [41]. The ingredients of proprietary Chinese medicine are relatively fixed and easy to use. The ingredients of Chinese patent medicines (CPM) are relatively fixed and easily applied, and some trials focusing on CPM have been conducted, including when-qi-fu-zheng injection, compound Radix Sophorae flavescence injection, and ai-shi injection [42]. From the above evidence, it can be concluded that TCM combined with chemotherapy can reduce the response to chemotherapy and improve the quality of life of patients.
who have completed radiotherapy and have not received western medicine treatment, the main pathogenesis is weakening physical resistance and excessive toxicity. Therefore, in this period, the use of improved Reed stem decoction to solve the toxicity and enhance the body resistance can effectively reduce the adverse reactions caused by radiotherapy [19].

To sum up, radiotherapy can be combined with TMR, which can effectively improve the survival rate of SCLC patients. After radiotherapy, we can choose TCM treatment, which can delay cancer recurrence and cancer cell metastasis, and bring survival benefits to patients [47].

TCM combined with Molecular targeted Therapy
In recent years, with the gradual accumulation of clinical research data of SCLC and the in-depth study of the pathological mechanism of SCLC, clinical trials of targeted therapeutic drugs such as anti-angiogenesis inhibitors and receptor tyrosine kinase inhibitors are underway, among them, Notch signal pathway inhibitors have achieved good results in phase I and II clinical trials of SCLC, while phase III clinical trials are still underway [48]. In the study of common acquired drug resistance in SCLC, a study on xenotransplantation models suggests that the combination of EZH2 and SLNFn11 can be used as a potent therapeutic strategy to enhance the effectiveness of standard therapy in the treatment of SCLC [49, 50], TCM can assist molecular targeted therapy and play a role in improving the immune function of patients with SCLC, mainly involving T cell subsets, natural killer cells, interleukin (IL)-4, IL-13, tumor-associated macrophages, and other cellular immune components. In addition, Fiji Powder, a TCM, has the effect of tonifying qi and nourishing yin, promoting blood circulation, and removing blood stasis, which can reduce some clinical adverse reactions and significantly increase the number of white blood cells, to improve patients' immune function and improve their quality of life [51].

Clinical and basic studies have proved that the compound prescription of TCM based on the principle of Fu zheng Jiedu can improve the acquired drug resistance of molecular targeted therapy. The advantage of TCM lies in its overall regulation, combined with molecularly targeted drugs focusing on precision treatment, it is possible to play a macro and micro synergistic effect and become an innovative model for the treatment of SCLC [52], NSCLC has achieved remarkable results in targeted therapy, but SCLC may have limited the exploration of molecular targets due to the limitations of treatment and the complexity of its molecular mechanism. Some studies have mainly focused on anti-angiogenesis, among which bevacizumab is a widely studied Vascular Endothelial Growth Factor (VEGF) inhibitor [53]. In a clinical study of stage II ES-SCLC patients conducted by Spigel et al, EP regimen combined with bevacizumab was used as the first-line and maintenance therapy group, and EP regimen combined with placebo was used as the control group. The median progression-free survival (PFS) of the two groups was 5.5 months and 4.4 months, but the median survival time was 9.4 months and 10.9 months, respectively, and the difference is not statistically significant (P > 0.05) [24, 53, 54]. From the above evidence, it can be concluded that TCM combined with molecular targeted therapy can improve the immune function of patients and improve their quality of life.

TCM combined with immunotherapy
The recurrence-prone characteristic of SCLC leads to a poor prognosis of SCLC, and the 2-year overall survival (OS) is less than 5%. United States Food and Drug Administration (FDA) has approved programmed cell death ligand 1 (PD-L1) antibody atezolizumab combined with carboplatin and etoposide as the first-line treatment for SCLC. FDA has approved programmed cell death 1 (PD-1) antibody monocular antibodies nivolumab and pembrolizumab as the third-line treatment of SCLC. As a result, immunotherapy breaks the deadlock in the treatment of SCLC in the past 30 years and brings more hope for patients with SCLC [55]. Studies have shown that the immune-suppressive state of SCLC seems to be related to tumor mutation burden (TMB), and the decrease of TMB can alleviate the immunosuppressive state [56]. Radiotherapy and chemotherapy can reduce the TMB of SCLC, alleviate the immunosuppressive state of the body, and improve the sensitivity of follow-up SCLC to immunotherapy. At present, there are no reliable predictive markers for immunotherapy in SCLC patients. Combined with previous studies, TMB seems to be more meaningful than PD-L1 expression in terms of predictive value, but there is a lack of a reliable research team. Other indicators, such as the T cell-inflamed gene-expression signature and the expression level of PD-L1 at tumor-stromal cell contact sites, have shown in some experiments that they have potential predictive value for ICIs prolongation of OS or PFS in patients with SCLC. However, they are limited to the small number of research and analysis, and there is a certain population bias, so further research and analysis of a large sample population are needed [57, 58]. The effect of immunotherapy combined with TMR is more significant than that of immunotherapy alone. Ganoderma lucidum polysaccharides can increase the ratio of effector T cells to Treg cells, thus relieving the inhibition of Treg cells on effector T cells [59]. Echinacea can reduce the number of CD4+ CD25+ Foxp3+ Treg cells, weaken its inhibitory effect, enhance the presentation function of antigen-presenting cells, and indirectly inhibit the function of Treg cells [60]. Professor Jia Yingjie proposed that the most frequently used drugs before and after immunotherapy were Radix Astragali and Trichosanthes [61]. Before immunotherapy, most of them are drugs for clearing heat, clearing phlegm, tonifying qi, and there is no lack of products for nourishing blood and dispelling blood stasis; after immunotherapy, we also pay attention to clearing lung and resolving phlegm, and the application of Qi regulating and stomach drugs are relatively more [62]. Compared with radiotherapy and chemotheraphy, before and after immunotherapy, based on invigorating qi and strengthening qi, more attention is paid to the application of dispelling qi and nourishing blood and nourishing substances, as well as detoxification and removing blood stasis. In Sun Yidan's study, the 1-year, 2-year, and 3-year survival rates of 305 SCLC patients were 51.0%, 12.2%, and 4.2% respectively, and the median OS was 13.0 (9.0–20.0) months. Moreover, a variety of laboratory indicators that can reflect tumor growth, inflammation and immune status and the proportion of lymphocyte subsets (NLR (P < 0.003), PLR (P = 0.001), ALI (P = 0.001), SII (P = 0.003), CEA (P < 0.001), CYFRA21-1 (P = 0.001)) (P < 0.05)) [62]. Thus, compared with the routine western medicine immunotherapy, TCM combined with immunotherapy can significantly improve the survival rate of SCLC patients and prolong the life span of patients.

TMR has great potential for tumor immune regulation, but its effective components and specific mechanism have not been fully elucidated, and the current research on the treatment of SCLC is very scarce, so it is necessary to further study [63].

Conclusion
In recent years, surgery, radiotherapy and chemotherapy, and molecular targeted therapy have played an important role in the treatment of SCLC, and they are also in continuous development and progress. However, in the process of treatment, conventional western medicine treatment has some limitations, and it will produce many toxic and side effects that affect the quality of life of patients. Patients often cannot bear to reduce the dose, stop medication or even stop treatment due to poor compliance, but TCM can make up for this disadvantage. It is mainly reflected in the following aspects: (1) The treatment of SCLC with TCM is mainly based on syndrome differentiation and the combination of disease differentiation and syndrome differentiation. The treatment methods and drug dosage vary from person to person. TCM treatment has certain advantages in improving patients’ symptoms, improving quality of life, optimizing cost effect, reducing toxicity and increasing efficiency, and effectively prolonging the survival time of patients. (2) TCM treatment can be used in most stages of SCLC treatment. We believe that the exploration of the treatment of integrated traditional Chinese and western medicine still needs to be carried out on a solid and innovative
theoretical basis, and we need to carry out forward-looking, multicenter, large-sample evidence-based medicine research, and gradually establish a reasonable and standardized modern tumor diagnosis and treatment system with individual diagnosis and treatment as the main body. We believe that through the complementary advantages of TCM and western medicine in diagnosis and treatment, the treatment of SCLC will continue to make a breakthrough [6, 64].

References

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