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Original Article

The effect of strengthening and consolidating body resistance combined with chemotherapy on immune function of patients with small cell lung cancer

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Abstract: Objective: To observe the effect of combination treatment with strengthening and consolidating body resistance and chemotherapy on immune function of patients with advanced small cell lung cancer (SCLC). Methods: A total of 150 patients with pathologically confirmed advanced SCLC admitted to Radiation Chamber of Linyi Central Hospital during the time between June 2012 and June 2017 were randomly divided into two groups: the group (80 patients) receiving just chemotherapy (the chemo group), and the group (70 patients) receiving combination treatment with strengthening and consolidating body resistance and chemotherapy (the combination group). After three months of the treatment, comparisons between the two groups were made in aspects including: levels of CD_4^+ T cell, CD_8^+ T cell in peripheral blood (PB), CD_4^+/CD_8^+ ratio changes, concentrations of serum interleukin-2 (IL-2), interleukin-6 (IL-6) and tumor necrosis factor (TNF-α), clinical efficacy and adverse drug reaction rate (ADR). Results: One month after chemotherapy, levels of PB CD_4^+ T cell, CD_8^+ T cell, CD_4^+/CD_8^+ T cell in patients of the combination group were higher than patients of the chemo group (P=0.038, P=0.044, P=0.035), which continued in 2 months later (P=0.040, P=0.034, P=0.048); and 3 months later (P=0.025, P=0.020, P=0.035); IL-2, IL-6, TNF-α levels were also obviously higher in the combination group 1 month after chemotherapy (P=0.030, P=0.024, P=0.043), and 2 months later (P=0.044, P=0.012, P=0.048); and 3 months later (P=0.008, P=0.001, P=0.005). Compared with the chemo group, the combination group's alimentary canal ADR rates dropped remarkably down (P=0.031), so did their excessive hair loss rates (P=0.004) and liver and kidney toxicity rates (P=0.025). Conclusion: Combination treatment with strengthening and consolidating body resistance and chemotherapy for SCLC can improve treatment efficacy and patients' immune function and decrease toxic side effects.

Keywords: Small cell lung cancer, supporting healthy energy, chemotherapy, immune function

Introduction

Lung cancer incidence rate is climbing up year by year. According to statistics, it has surpassed liver cancer and became the top 1 deadliest tumor in China, accounting for 22.7% deadly malignant tumors [1, 2]. Morbidity of male lung cancer patients in China has exceeded 500,000 and female patients is reaching 400,000 [3]. There are two major types of lung cancer: small cell lung cancer (SCLC), also known as oat cell carcinoma, makes up about 20% lung cancers. SCLC tumor cell multiplies rapidly in short time along with endocrine dyspraxia or carcinoid syndrome [1]; non SCLC is a high morbidity type and makes up almost 80% of lung cancers [4, 5]. Though SCLC type's morbidity is lower than non-SCLC, its malignancy is higher. So far, chemotherapy has been the first treatment recommended. Scholars overseas insist operation at first and then chemotherapy for stage I and II SCLC; while domestic scholars incline to chemotherapy-centered combination therapy, namely chemotherapy at first, then radiotherapy or operation, and chemotherapy at last. For stage III and IV SCLC, domestic and oversea scholars prefer chemotherapy or/with palliative radiotherapies, but such treatment in most cases cannot live up to patients' expectation [6]. Therefore, further study on SCLC is needed to improve efficacy. SCLC treatment to date is mainly systemic chemotherapy. Although it increases survival rate, its effect on patients' immune function and adverse drug reaction

rate (ADR) is yet clear. Inflammatory mediator and immune cell, as the critical constituents of tumor regional environment, are significant to morbidity and maturation of SCLC [7, 8]. Since tumor immunity is mainly cell-mediated immunity, this study is going to test T cell or its subgroup to tell patients' prognosis [9, 10].

Strengthening and consolidating body resistance can adjust body function, support healthy energy, decrease toxic side effects caused by radiotherapy, chemotherapy, improve treatment efficacy, prolong survival time, etc. [11, 12]. However, there's no in-depth study on using strengthening and consolidating body resistance in SCLC treatment yet. This study is going to discuss efficacy and safety of treating SCLC with strengthening and consolidating body resistance and chemotherapy, and its effect on T cell or its subgroups in SCLC patients.

Materials and methods

General materials

This research was approved by the Ethic Committee of Linyi Central Hospital. All patients had signed informed consent.

A total of 150 advanced SCLC patients verified by rapid intraoperative pathological diagnosis admitted to Linyi Central Hospital during the time between June 2012 and June 2017 were chosen as objects of this study and were randomly divided to two groups: the group (80 patients) receiving just chemotherapy (the chemo group), and the group (70 patients) receiving combination treatment with strengthening and consolidating body resistance and chemotherapy (the combination group). All patients aged 35-75 years old. Mean age of the two groups were respectively (65.3±5.8) and (67.3±3.2) years old.

SCLC pathological type: Oat cell type, intermediate cell type and mixed oat cell type [13].

Pathological type: SCLC staging in this study is in conformity with the VA staging system developed jointly by The Veterans' Administration Lung Study Group and International Association for the Study of Lung Cancer which classifies SCLC into two stages: limited stage and extensive stage. Limited-stage SCLC is characterized by tumor limited in side-thorax, including on clavicle or scalene lymphonodus metastasis and same side pleural effusion. Limited-stage SCLC shall be further classified by TNM staging, so as to perform the best customized therapy on patients of different stages. Extensive-stage SCLC, on the other hand, is featured by lesion exceeds the coverage of limited-stage [14].

Karnofsky Performance Status (KPS): Performance status evaluation standard was proposed by Karnofsky from Eastern Cooperative Oncology Group. Based on patients' capability of daily life, conditions and self-managing ability, KPS ranking runs from 100 to 0 with standard interval of 10, where 100 is "perfect" health and 0 is death. The higher the score goes, the better health the patients are in and higher tolerance they have for side effects coming along with treatment and thus higher probability of going through thorough treatment. On the contrary, the lower the score is, the worse health the patients are in and lower tolerance they have. If the score is lower than 60, numerous effective antineoplastic therapies cannot be performed [15].

Inclusion criteria: Pathologically verified as SCLC; stage III and IV patients who went through excision; aged 35-75.

Exclusion criteria: Patients suffering from severe heart, lung, liver or kidney diseases; or other kinds of lung cancer; patient with mental illness; patients with shock from severe infection; patients went through post-operative radiotherapy; patients for whom supporting healthy energy therapy is contraindicated: whole-body tumor metastasis.

Treating methods

Operative treatment: The resection on lesion lung lobe or pneumonectomy and lymphonodus was performed according to preoperative imaging materials like CT, MRI and intraoperative frozen section.

Chemotherapy regimens: It was started 3 weeks after the operation. Patients in the chemo group were given intravenous injection of paclitaxel 80 mg/kg since chemotherapy day 1; intravenous injection of cisplatin 25-30 mg/m^2 from day 1 to day 3; course of treatment was 1 month. Medication was the same for 3 consecutive courses. During chemotherapy, patients were given palliative care like intravenous nutri-

Table 1. Comparison of general data of the two groups (n, %)

Groups	Age	Gender		Pathological type			Stage		KPS
		Male	Female	Oat cell type	Intermediate cell type	Compound oat cell type	III	IV	
Chemotherapy group (n=80)	65.3±5.8	55	25	25 (31.25)	36 (45.00)	19 (23.75)	48 (60.00)	32 (40.00)	58.2±14.2
Associated group (n=70)	67.3±3.2	48	22	18 (25.71)	32 (45.71)	20 (28.57)	37 (52.86)	33 (47.14)	52.9±16.7
t/X^2	-0.523	0.001			0.737		0.512		-0.248
P	0.476	0.981			0.692		0.474		0.867

Notes: KPS: Karnofsky Performance Score.

Table 2. Total effective rates of the two groups after treatment

Groups		Significant improvement	Some improvement	Invalid	Overall efficiency (%)	X^2	P
Chemotherapy group (n=80)	Cough	23	27	30	62.50	4.704	0.030
	Coughing up phlegm	24	23	33	58.75	4.936	0.026
	Shortness of breath	29	24	27	66.25	6.600	0.010
	Lacking in strength	20	25	35	56.25	15.700	0.000
Associated group (n=70)	Cough	20	36	14	80.00		
	Coughing up phlegm	23	31	16	77.14		
	Shortness of breath	27	33	10	85.71		
	Lacking in strength	35	26	9	87.14		

tion to protect liver and stomach. When there was any ADR, symptomatic treatments were given right away. When there was severe alimentary canal ADR, patients were given metoclopramide and dolasetron to stop vomitting, and Bao Fei Tai to protect liver and kidney after chemotherapy.

Patients in the combination group had, in addition to what those in the chemo group received, oral strengthening and consolidating body resistance: (prescription: astragalus 30 g, ginseng 20 g, glossy privet fruit 30 g, radix glehniae 10 g, notoginseng powder 6 g, rhizoma atractylodis macrocephalae 15 g, radix ophiopogonis 15 g, safflower 15 g, semen coicis 30 g, ultrapure water 1,000 mL, boiled for 30 min till there was only 100 mL, which is a one-time dose), once in the morning and night. This medication started from chemotherapy day and continued till the end of 3 courses without withdrawal. When there was any ADR, symptomatic treatments were timely given.

Observation indicators

Key observation indicators: Peripheral blood T cell and ratio test: Fasting peripheral blood (PB) 5 mL were collected in EDTA anticoagulation tube from patents and analyzed using flow cytometry (FCM), depending on the T cell subgroups to be detected, corresponding fluorescent marked monoclonal antibodies (CD_4, CD_8 signs made by Cell Signaling company, 1X fetal bovine serum PBS diluted to 0.5%) were add, and slightly mixed evenly, standing in incubation in dark place for 15 min at room temperature. Then 1 mL of red blood cell lysis buffer was added, standing in dark place for 10 min. Centrifuging upon confluent lysis of red blood cell, supernate was discarded, and then it was deterged 3 times with PBS, and another 1mL PBS was added It was tested with FCM, and equipment-embedded software was used to analyze CD_4^+ T lymphocyte and CD_4^+/CD_8^+ T lymphocyte ratio changes and trends.

Measurement of serum inflammatory factors: Patients' fasting PB was collected in EDTA anticoagulation, standing for 2 h. Then it was centrifuged at high speed and low temperature, separating upper plasma and collecting. The instructions on ELISA kit (IL-2: MAB602, R&D company; IL-6: MAB206, R&D company; TNF-α: AF-210-NA, R&D company) was followed to detect the OD value of serum IL-2, IL-6, TNF-α of patients from both groups and calculate concentration of the above three inflammatory factors according to standard curve.

Secondary observation indicators: Symptom improvements: Symptoms include coughing, coughing of phlegm, shortness of breath, lacking in strength.

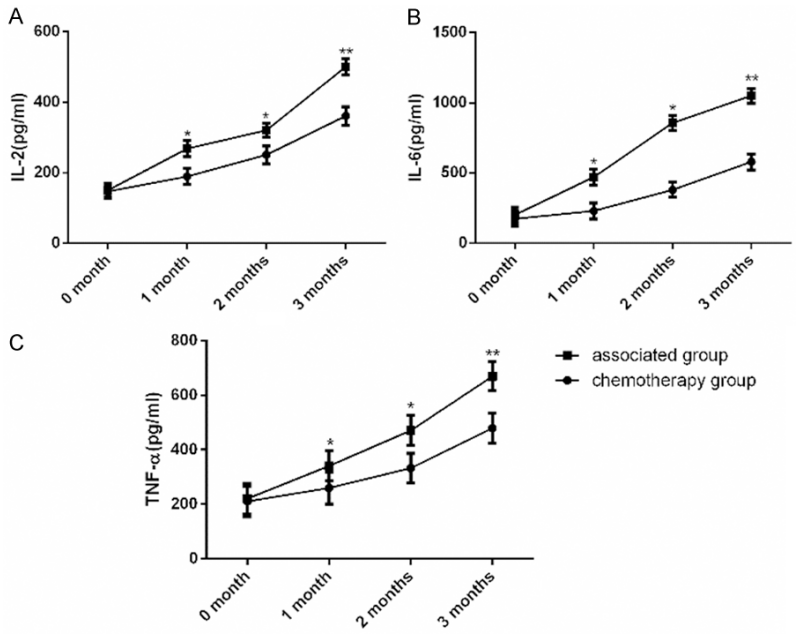

Figure 1. Comparison of serum IL-2, IL-6, TNF-α concentration changes in patients of the two groups. Comparison between groups at the same time, *P<0.05; **P<0.01. 0 month: Chemotherapy before; 1 month: One month after chemotherapy; 2 months: Two months after chemotherapy; 3 months: Three months after chemotherapy. IL-2, serum interleukin-2; IL-6, interleukin-6; TNF-α, tumor necrosis factor.

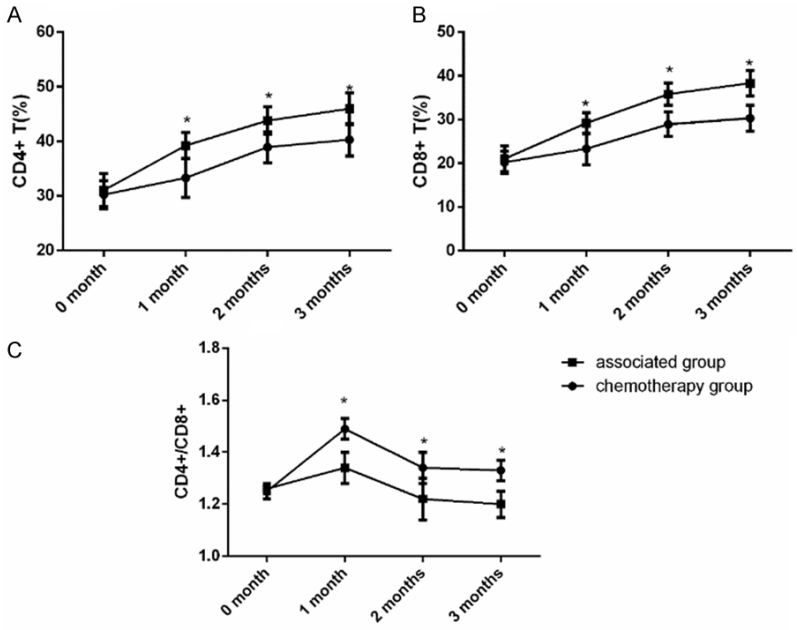

Figure 2. Comparison of T cell levels and CD_4^+/CD_8^+ ratio changes of the two groups. Comparison between groups at the same time, *P<0.05. 0 month: Chemotherapy before; 1 month: One month after chemotherapy; 2 months: Two months after chemotherapy; 3 months: Three months after chemotherapy.

Effectiveness: Distinctly better, partly better, ineffective. Distinctly better means symptoms listed above disappear or appear occasionally (once or twice a week) during the chemotherapy. Partly better refers to that coughing and coughing with phlegm graded between moderate and severe, along with shortness of breath and drowsiness. Moderate: Lesion exceeds lung lobe, but limited to one side; coughing, coughing up phlegm, and hemoptysis to different degrees now and then; recurrent lung infection; X-ray chest film shows there's honeycomb shadow on lung lesion, and there's moist rale by auscultation. Severe: Lung at two sides show lesion, having fever and coughing, coughing up thick and yellow phlegm, chest distress and shortness of breath, usually along with acropachy, different degrees of hemoptysis, even large hemoptysis and recurrent lung infection. No effective refers to high daytime and night time cough frequency, phlegm in large amount and thick, shortness of breath and drowsiness. Total effective rate=CR + PR/total patients * 100%.

ADR: Digestive system symptoms include nausea and vomiting; excessive hair loss: 30% loss of total hair; liver and kidney toxicity: liver function index (glutamic-pyruvic transaminase >100 U/L, glutamic oxalacetic transaminase >100 U/L, direct bilirubin >4.5 mg/L, TBil (total bilirubi) >34 μmol/L) and kidney function (creatinine >100 μmol/L, urea nitrogen >9 mmol/L) [16].

Table 3. Comparison of ADR rates of the two groups

Groups	Gastrointestinal symptoms	Serious hair loss	Toxicity of Liver and kidney
Chemotherapy group (n=80)	24 (30.00%)	20 (25.00%)	15 (18.75%)
Associated group (n=70)	10 (14.30%)	5 (7.14%)	4 (5.71%)
χ^2	5.224	8.514	5.697
P	0.031	0.004	0.025

Note: ADR, adverse reaction rate.

Statistical analysis

All the measurement data were expressed by mean ± standard deviation (mean ± sd), and analyzed by SPSS17.0. Measurement data of both groups conformed to normal distribution, and were examined by independent sample t test. Enumeration data, on the other hand, were examined by chi-square test and Fisher's exact test and expressed by chi-square. All the figures and tables were analyzed and produced by Graphpad Prism 5.0. Inspection level α= 0.05.

Results

Comparison of general data of the two groups

The chemo group consisted of 80 patients and the combination group of 70 patients. Differences of their age, sex ratio, pathological types, stages and post-operation Karnofsky performance status scales were of no statistical significance (all P>0.05). See **Table 1**.

Symptom improvement efficacy

At the end of the treatment, improvement rates on respiratory symptoms: cough, cough with phlegm, shortness of breath were obviously lower in chemo group than that in the combination group (P=0.030, P=0.026, P=0.010), so was the improvement rate on constitutional symptoms: drowsiness (P=0.000). See **Table 2**.

Effect on serum cytokines

During observation period, levels of IL-2, IL-6, TNF-α were obviously higher in the combination group than the chemo group 1 month (P=0.030, P=0.024, P=0.043), 2 months (P=0.044, P= 0.012, P=0.048) and 3 months (P=0.008, P=0.001, P=0.005) after chemotherapy. See **Figure 1**.

Effect on immune cells

During observation period, levels of PB CD_4^+ T cell, CD_8^+ T cell and CD_4^+/CD_8^+ T cell after chemotherapy in patients of the combination group were higher than patients of the chemo group (1 month: P=0.038, P= 0.044, P=0.035; 2 months: P=0.040, P=0.034, P=0.048; 3 months: P=0.025, P=0.020, P= 0.035). See **Figure 2**.

Comparison of main ADR rates of the two groups

Compared with the chemo group, the alimentary canal ADR rates in combination group remarkably dropped (P=0.031), so did hair loss rates (P=0.004), and liver and kidney toxicity (P=0.025). See **Table 3**.

Discussion

Human body's immune state, especially cell-mediated immunity, is closely associated with the occurrence and development of tumor; and in cell-mediated immunity, T lymphocytes is a significant immunocompetent cell. CD_4^+ CD_8^+ T cell subgroups and the cytokines they secreted not only directly mediate cell immune function, but also are critical to adjustment of immune response. They, together with NK cell and B cell-mediated humoral immunity, constitute the principal part of tumor immunity - one of the important functions of CD_4^+, CD_8^+ T cell-mediated cellular immunity [17]. In traditional Chinese medicine, strengthening and consolidating body resistance is mainly effective at tonifying qi and yin, strengthening the spleen and stomach, and dispersing blood stasis and removing qi stagnation, clearing away heat and toxic materials, and improving immunity [18, 19]. Research findings demonstrate that combination of strengthening and consolidating body resistance and chemotherapy has better effect for malignant tumor patients than chemotherapy alone. For instance, Liu et al. found that combination of strengthening and consolidating body resistance and chemotherapy exerted better effect on bone metastasis and esophagus cancer than chemotherapy alone, which is in consistence with this study: strengthening and

consolidating body resistance can help lift SCLC patients' immunity after chemotherapy and total effective rate of therapy [20, 21]. This is probably associated with that astragalus directly kills tumor cell, and further induces cell apoptosis; ginsenoside Rh2 has antineoplastic effect; Notoginseng powder increases accumulation of antitumor ingredient in tumor cell and augment efficacy thereby [22, 23].

T lymphocyte plays an important role in adjusting specific immunity, nonspecific immunity, cell-mediated immunity and humoral immunity. Substantial evidence proves that helper T cell is closely related to the imbalance of inflammatory factors and incidence and development of tumors [24]. Inflammatory factors participate in cell migration and transformation, localize foreign matters and facilitate granulocyte's bactericidal effect and phagocytic ability. Strengthening and consolidating body resistance not only has distinct combined antineoplastic effect, but also improves immune cell functions [11, 25]. Research by Yang et al. found that combination of strengthening and consolidating body resistance and radiotherapy enhanced immunity of tumor-bearing mice; it enhances, compared with radiotherapy alone, abdominal macrophage's phagocytic ability in tumor-bearing mice, improves thymus and spleen index of tumor-bearing mice; inhibits the decrease of serum IL-2, IL-6 and TNF-α in tumor-bearing mice caused by chemotherapy as well as their decrease in PB cell caused by radiotherapy, increases amount of CD_4^+ T cell and CD_8^+ T cell and enhances surface killing effect [12, 21, 26]. This might be due to that astragalus can increase total amount of leukocyte, boost bactericidal ability of neutrophile granulocyte and phagocyte's phagocytic ability [26]. Astragalus can boost protein synthesis and energy metabolism, improve body immunity, and induce production of leukocyte interleukin [27, 28].

Besides, chemotherapy drugs prominently kill normal cells and damage other organ functions. Excessive hair loss, liver and kidney toxicity and side effects on digestive system after chemotherapy not only aggravate the disease, but also cause psychological and emotional damages to them, thus slowing down cure of cancer [29, 30]. In prescription of strengthening and consolidating body resistance, angelica sinensis and radix paeoniae alba nourish blood; sang, astragalus, red dates invigorate qi and strengthen the spleen, support healthy energy, pericarpium citri reticulatae, pinellia ternate and fritillaria thun-bergli regulate qi-flowing for eliminating; licorice root plays the role of adjusting the other elements so as to exert effect of tonifying qi, strengthening the body resistance, nourishing blood and consolidating body resistance, which is effective at easing whole-body side effects [31]. This study showed that strengthening and consolidating body resistance could reduce incidence of side effect and improve total effective rate.

In this research, clinical efficacy and mechanism of strengthening and consolidating body resistance had been studied, but yet reported. However, few objects were included in this study, which limits the further result analysis. We will further discuss in depth how strengthening and consolidating body resistance improve SCLC patients' conditions through adjusting cell-mediated immunity.

In conclusion, combination treatment with strengthening and consolidating body resistance and chemotherapy for SCLC can improve treatment efficacy and patients' immune function, and decrease toxic side effects.

Disclosure of conflict of interest

None.

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