ORIGINAL RESEARCH

Impact of Shenmai Injection Combined with Chemotherapy on T-cell Subsets and Cytokine Profiles in Patients with Advanced Non-Small Cell Lung Cancer

Jianping Jiang, MM; Weiqiang Mo, MM; Xue Lian, MM; Xiaoyan Jin, MM; Haiying Cheng, MM

ABSTRACT

Background • Non-small cell lung cancer (NSCLC) represents a significant portion of lung cancer cases, with a poor prognosis and limited treatment options for advanced stages. Enhancing the effectiveness of chemotherapy through adjunctive therapies is a critical area of research.

Objective • To evaluate the effect of Shenmai injection combined with chemotherapy on T-cell subsets and cytokine expression in patients with advanced NSCLC.

Methods • A comparative prospective study was conducted, and a total of 96 patients with advanced NSCLC were selected. Patients were divided into two groups based on different chemotherapy regimens: an observation group (48 patients) receiving Shenmai injection combined with chemotherapy and a control group (48 patients) receiving chemotherapy alone. The study measures and compares the levels of T-cell subsets ($CD3^+$, $CD4^+$, $CD4^+/CD8^+$) and cytokines (IL-2, IL-4, IL-5, IL-6, TNF-α, IFN-γ, VEGF, bFGF, CA125, and CEA) before and after treatment in both groups. Statistical analysis was performed on the collected data.

Results • Significant changes were observed in the levels of T-cell subsets and cytokines before and after chemotherapy in both groups ($P < .05$). Compared with the control group, the observation group exhibited significant improvement in T-cell subsets $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ ($P < .05$). Furthermore, the levels of cytokines IL-2, IL-4, IL-5, IL-6, TNF-α, IFN-γ, VEGF, bFGF, CA125, and CEA were significantly lower in the observation group compared to the control group (all $P < .05$).

Conclusions • Shenmai injection combined with chemotherapy enhances the cellular immune function in patients with advanced NSCLC. This combination therapy not only reverses tumor progression but also improves the overall therapeutic effect, suggesting a promising adjunctive treatment strategy for advanced NSCLC. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases. The rising incidence and mortality rates of NSCLC are attributed to various factors, including environmental degradation, increased exposure to ionizing radiation, and a higher prevalence of occupational carcinogens.[1,2] It highlights the urgent need for effective therapeutic strategies to manage and treat advanced stages of NSCLC.[1] Unfortunately, the early symptoms of NSCLC frequently manifest subtly, and a considerable portion of the Chinese population lacks adequate health awareness. Therefore, the diagnosis of many patients occurs at an advanced stage, depriving them of the opportunity for potentially curative surgical intervention during the optimal timeframe.[2]

Chemotherapy can offer some relief for patients with advanced NSCLC, enhancing their quality of life and extending survival to a certain extent. However, these patients are typically in a weakened state, and the toxic side effects of chemotherapy can further compromise their immune function, leading to alterations in cytokine expression.[2,3] As a result, a significant number of patients may find it challenging to tolerate and complete the full course of chemotherapy, which can have a detrimental impact on their prognosis.

Several clinical studies have suggested the synergistic effect of integrating traditional Chinese medicine (TCM) with chemotherapy, effectively mitigating the toxic side effects associated with chemotherapy. This combined approach not only enhances patient tolerance and ensures

the completion of chemotherapy but also elevates the overall quality of life for individuals with advanced NSCLC. The primary treatment approach for advanced NSCLC predominantly involves chemotherapy, which is frequently supplemented with TCM interventions. These interventions aim to enhance the body's vital energy (*qi*), nourish the body's essential elements (*yin*), and strengthen the overall health of the body and its blood vessels.[3,4]

Shenmai injection, a TCM formulation, comprises *Ginseng* and *Ophiopogon* root extracts, known for their immune-modulating properties and potential synergistic effects with chemotherapy.[4] Therefore, the objective of this study was to examine the impact of Shenmai injection, combined with chemotherapy, on cellular immune function and cytokine profiles among patients diagnosed with advanced NSCLC undergoing chemotherapy. Our findings offer novel insights into adjunctive therapies for patients with advanced NSCLC undergoing chemotherapy.

MATERIALS AND METHODS

Study Design

The study employed a prospective cohort design to investigate the impact of Shenmai injection combined with chemotherapy on cellular immune function and cytokine profiles in patients with advanced NSCLC. A total of 96 patients admitted to The Second Affiliated Hospital of Jiaxing University's Oncology Department between January 2020 and December 2022 were included. Patients were divided into an observation group (n=48) receiving Shenmai injection alongside chemotherapy and a control group (n=48) undergoing chemotherapy alone. General characteristics were comparable between the groups ($P > .05$, Table 1), ensuring a balanced comparison.

Inclusion and Exclusion Criteria

The inclusion criteria were defined as follows: (1) histologically confirmed NSCLC; (2) TNM stage IB or IV, as per the 7th edition of the Union for International Cancer Control (UICC) staging system; (3) Karnofsky Performance Status (KPS) score >60; (4) anticipated survival of more than 6 months; (5) absence of prior radiotherapy, chemotherapy, or TCM treatment; and (6) provision of informed consent by both patients and their families.

The exclusion criteria comprised: (1) lack of a confirmed pathological diagnosis; (2) prior use of immunomodulatory agents; (3) presence of cardiopulmonary insufficiency, severe liver or kidney dysfunction, or other significant medical complications; (4) pregnancy or lactation; and (5) inability to complete a minimum of 2 cycles of chemotherapy.

Treatment Regimens

All patients underwent chemotherapy, with the regimens consisting of TP, EP, CAP, GP, MVP, and NP. Moreover, patients in the observation group received Shenmai injection (100 mL) intravenously once daily for seven consecutive days, commencing one day before the initiation of chemotherapy.

T-Cell Subset Analysis

Peripheral venous blood samples (3-5 mL) were obtained from patients in both groups one day before the initiation of the first chemotherapy cycle and upon completion of four cycles of chemotherapy. T-lymphocyte subsets, including $CD3^+$, $CD4^+$, and $CD8^+$ cells, were quantified utilizing a BeamCyte flow cytometer (Changzhou Bidako Biotechnology Co., Ltd.). All procedures strictly adhered to the manufacturers' instructions. The rate of change (Δ) for each index was calculated using the following formula to evaluate changes in cellular immune function: $Rate\ of\ Change\ (\Delta) = (value_{\ after\ 4\ cycles} - value_{\ before\ treatment}) / value_{\ before\ treatment}$

Evaluation of Treatment Efficacy

The predictive impact of alterations in T-lymphocyte subsets on short-term treatment response was assessed. "Complete response," "partial response," and "stable disease" were classified as "effective" outcomes, whereas "progressive disease" was categorized as "ineffective."

Cytokine Profiling and Assessment

Peripheral venous blood samples (3-5 mL) were obtained from patients in both study groups one day prior to the initiation of the first chemotherapy cycle and one week following the completion of two cycles of chemotherapy. The levels of IL-2, IL-4, IL-5, IL-6, TNF-α, IFN-γ, VEGF, bFGF, CA125, and CEA in the peripheral blood were quantified using enzyme-linked immunosorbent assay (ELISA). All experimental procedures strictly adhered to the manufacturer's protocols.

Statistical Analysis

Data analysis was performed using SPSS version 23.0 software (International Business Machines, Corp., Armonk, NY, USA). Measurement data are presented as mean ± standard deviation ($\bar{x} \pm s$) and were analyzed utilizing the *t* test.

Table 1. Baseline Characteristics of Patients in the Observation and Control Groups

Indicators		Observation Group	Control Group	t/χ^2	*P* value
Number of cases (case)		48	48		
Age (years)		28.90±10.80	29.20±11.30	1.460	.072
Gender (male)		14 (2917)	16 (33.33)	0.194	.660
Duration (months)		3.84±1.07	3.79±1.34	0.940	.855
Types of Pathology	Ringworm cancer	8 (16.67)	7(14.58)		
	Adenocarcinoma	10 (20.83)	14 (29.17)		
	Large cell carcinoma	3 (6.25)	2 (4.17)		
	Other	27 (56.25)	25 (52.08)	1.010	.799
Body mass index (BMI, kg/m²)		33.36±6.94	32.54±4.97	0.582	.280
Comorbidity	History of Hypertension	2169 (29.99)	1329 (27.99)	5.551	.684
	History of Diabetes Mellitus	2169 (29.99)	1329 (27.99)	5.185	.975
	History of Smoking	2314 (32.00)	1614 (33.99)	1.949	.163
	History of Alcohol Consumption	1301 (17.99)	807 (17.00)	1.949	.163
	Irregular Life	3549 (49.07)	2360 (58.130)	0.457	.499

Note: This table presents the baseline characteristics of patients in the observation and control groups. Statistical analyses were conducted to compare the two groups, with *P* values indicating the significance of differences. No significant differences were found between the groups for any of the baseline characteristics ($P > .05$).

Table 2. Comparison of Changes in T Cell Subsets Before and After Treatment between the Observation and Control Groups [($\bar{x} \pm s$), %]

Indicators		Observation Group	Control Group	*t*	*P* value
Number of Cases (case)		48	48		
CD3⁺/ %	Before Treatment	58.31±5.12	58.45±5.31	0.132	2.845
	After Treatment	65.23±4.77	62.54±4.49	8.133	.003
CD4⁺/%	Before Treatment	30.25±4.24	31.11±3.73	1.055	.147
	After Treatment	44.56±4.35	37.54±4.49	7.780	.000
CD8⁺/ %	Before Treatment	28.03±3.08	27.84±3.06	0.303	.381
	After Treatment	21.31±3.12	24.36±2.92	4.944	.000
CD4⁺/CD8⁺	Before Treatment	1.26±0.19	1.28±0.15	0.572	.284
	After Treatment	1.75±0.21	1.44±0.17	7.949	.000

Note: Significant changes were observed in the detection results of T-cell subsets in both groups after treatment compared to before treatment ($P < .05$). This finding suggests a notable impact of the treatment on T-cell subsets in both groups, with statistical significance.

Table 3. Changes of T-Cell Subgroup for Prediction of Treatment Response in Patients

Indicators	The Cut-Off Value (%)	AUC	Sensitivity (%)	Specificity (%)	Youden index
ΔCD3⁺	8.69	0.881	84.97	77.28	62.34
ΔCD4⁺	22.31	0.867	71.54	100	71.64
ΔCD8⁺	18.49	0.794	62.64	64.84	56.84
ΔCD4⁺/ΔCD8⁺	27.58	0.918	77.81	94.15	82.15

Note: This table presents the cut-off values, the area under the curve (AUC), sensitivity, specificity, and Youden index for predicting treatment response based on changes in T-cell subgroup levels. A higher Youden index indicates a better diagnostic performance of the respective T-cell subgroup in predicting treatment response.

Categorical data are expressed as frequencies and percentages [n (%)] and were subjected to analysis using the chi-square test (χ^2). Statistical significance was set at a $P < .05$.

RESULTS

Comparison of T-Cell Subsets Before and After Treatment

Following four cycles of treatment, significant alterations were observed in the levels of CD3⁺, CD4⁺, CD8⁺, and CD4⁺/CD8⁺ T-cell subsets compared to baseline values in both study groups ($P < .05$). Moreover, the post-treatment values of these T-cell subsets demonstrated marked improvement in the observation group compared to the control group ($P < .05$), Table 2.

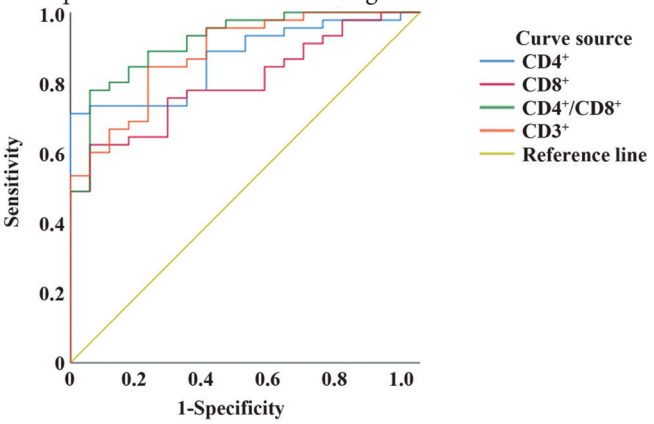
Predictive Value of T-Cell Subset Changes for Treatment Efficacy

In the observation group, the optimal cut-off values for predicting treatment response were determined to be 8.69% for ΔCD3⁺, 22.31% for ΔCD4⁺, 18.49% for ΔCD8⁺, and 27.58% for ΔCD4⁺/CD8⁺. The corresponding Youden indices were calculated as 62.34, 71.64, 56.84, and 82.15, respectively. Refer to Table 3 and Figure 1.

Comparison of Cytokines Between Groups

Table 4 presents the comparison of cytokine levels between the observation and control groups. Before treatment, there were no significant differences in IL-2, IL-4, IL-5, IL-6, IFN-γ, and TNF-α levels between the groups ($P > .05$). However, after treatment, significant differences were observed in IL-2 ($P = .001$), IL-4 ($P = .019$), IL-5 ($P = .001$), IL-6 ($P = .001$), IFN-γ ($P = .020$), and TNF-α ($P = .001$) levels between the groups.

Figure 1. ROC Curve Analysis for Predicting Short-Term Therapeutic Effect Based on Changes in T Cell Subsets



Note: ROC curve analysis was performed to assess the predictive value of changes in T cell subsets (ΔCD3⁺, ΔCD4⁺, ΔCD8⁺, and ΔCD4⁺/CD8⁺) for the short-term therapeutic effect in patients. The area under the curve (AUC) values and corresponding sensitivity, specificity, and Youden index are presented for each T-cell subset change.

Table 4. Comparison of Cytokine Levels Before and After Treatment in Two Groups ($\bar{x} \pm s$)

Indicators	Treatment Phase	Observation Group	Control Group	*t*	*P* value
Number of Cases (case)		48	48		
IL-2 (pg/mL)	Before Treatment	32.14±10.10	33.15±10.84	0.472	.319
	After Treatment	46.10±7.03[a]	40.23±9.47[a]	3.448	.000
IL-4 (pg/mL)	Before Treatment	46.38±11.45	46.81±11.35	0.185	.429
	After Treatment	34.21±12.06[a]	39.26±11.55[a]	2.095	.019
IL-5 (pg/mL)	Before Treatment	26.45±9.41	26.84±9.48	0.020	.420
	After Treatment	17.42±8.26[a]	21.14±9.87[a]	3.003	.000
IL-6 (pg/mL)	Before Treatment	40.48±5.69	39.65±6.24	1.026	.306
	After Treatment	18.96±4.73[a]	24.46±5.23[a]	8.143	.000
IFN-γ (pg/mL)	Before Treatment	46.31±12.21	46.26±11.96	0.021	.492
	After Treatment	58.16±15.14[a]	52.12±13.26[a]	2.028	.020
TNF-α (pg/mL)	Before Treatment	6.98 ± 1.05	6.88 ± 0.96	0.549	.584
	After Treatment	5.47 ± 0.71[a]	2.38 ± 0.31[a]	31.151	.000

[a]Significant difference ($P < .05$) compared with pre-treatment values. Values are presented as mean ± standard deviation.

Abbreviations: IL, interleukin; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha.

Table 5. Changes in Serum Tumor Cytokine Levels in the Two Groups

Indicators	Treatment Phase	Observation Group	Control Group	*t*	*P* value
Number of cases (case)		48	48		
VEGF (pg/mL)	Before treatment	522.40 ± 23.67	521.75 ± 25.05	0.131	.448
	After treatment	235.94 ± 15.92[a]	314.22 ± 14.48[a]	25.201	.000
bFGF (ng/L)	Before treatment	26.17 ± 3.52	25.86 ± 3.68	0.422	.337
	After treatment	14.79 ± 1.88[a]	18.17 ± 1.90[a]	8.761	.000
CA125 (U/mL)	Before treatment	138.90 ± 19.68	139.29 ± 20.40	0.095	.462
	After treatment	22.82 ± 4.03	65.75 ± 6.45[a]	39.107	.000
CEA (ng/mL)	Before treatment	16.86 ± 4.78	17.22 ± 4.70	0.372	.355
	After treatment	5.50 ± 1.61[a]	8.93 ± 2.62[a]	7.727	.000

[a]Significant difference ($P < .05$) compared with pre-treatment values. Values are presented as mean ± standard deviation.

Abbreviations: VEGF, Vascular endothelial growth factor; bFGF, Basic fibroblast growth factor; CA125, Cancer antigen 125; CEA, Carcinoembryonic antigen.

Notably, post-treatment levels of IL-2, IL-5, IL-6, IFN-γ, and TNF-α were significantly lower in the observation group compared to the control group ($P < .05$). These findings indicate a favorable modulation of cytokine profiles following Shenmai injection combined with chemotherapy.

Comparison of Serum Biomarkers Reduction

After treatment, there was a significant decrease in serum levels of VEGF, bFGF, CA125, and CEA in both study groups ($P < .05$). However, the reductions were more substantial in the observation group compared to the control group, with statistically significant differences noted ($P < .05$), refer to Table 5.

DISCUSSION

In TCM, lung cancer is classified into several syndromes, including "cough," "lung atrophy," "phlegm and fluid," "lung accumulation," "pulmonary mass," and "lung obstruction."[4] These classifications are based on the underlying etiology and pathogenesis, which involve factors such as *qi* and *yin* deficiency, disharmony between *yin* and *yang*, and the invasion of pathogenic factors into the lungs. These factors contribute to lung dysfunction, impaired ventilation, and stagnation of *qi* and blood.[5]

After conventional treatments like surgery, radiotherapy, and chemotherapy, patients with advanced lung cancer frequently exhibit deficiency syndromes and the persistence of pathogenic factors.[6] Therefore, an effective approach to lung cancer treatment should address both deficiency and excess patterns. Previous research has indicated that the primary etiology and pathogenesis of primary lung cancer often involve *qi* and *yin* deficiency. This deficiency arises as *qi* and *yin* are intricately connected, and treatments like radiation and chemotherapy can lead to the development of *qi* deficiency or *yin* and fluid deficiency.[7,8]

Cellular immunity plays a pivotal role in anti-tumor immune responses, with humoral immunity often acting synergistically.[9] In NSCLC, T cells, particularly $CD4^+$ and $CD8^+$ T cells, are the predominant immune cell types. However, chemotherapy, the primary treatment modality for advanced NSCLC, can impede immune function and harm normal cells, thereby compromising the patient's overall health and survival.

Shenmai injection, a TCM formulation comprising red *ginseng* and *Ophiopogon japonicus*, has been documented to possess immunomodulatory properties. *Ginseng* exhibits a biphasic effect on the immune system, while *Ophiopogon japonicus* polysaccharide has been found to enhance both humoral and cellular immune function and induce various cytokines.[10] Animal studies have demonstrated that *Ophiopogon japonicus* polysaccharide can restore immune organ damage and restore immune cell counts in immunocompromised mice.[11,12]

In this study, 96 patients diagnosed with advanced NSCLC undergoing chemotherapy were enrolled to explore the impact of Shenmai injection combined with chemotherapy on T-cell subsets and serum cytokines. The findings revealed a significant enhancement in $CD3^+$, $CD4^+$, and the $CD4^+/CD8^+$ ratio with the addition of Shenmai injection to chemotherapy compared to chemotherapy alone. Moreover, post-treatment serum levels of VEGF, bFGF, CA125, and CEA were notably reduced in the Shenmai injection group in comparison to the chemotherapy-only group.

The results of this study demonstrated that combining Shenmai injection with chemotherapy significantly altered cytokine levels. Specifically, the levels of IFN-γ, TNF-α, and IL-2 increased, while the levels of IL-6 and IL-10 decreased. These differences were statistically significant compared to the control group receiving chemotherapy alone ($P < .05$). Previous research[12] has indicated that in NSCLC, chemotherapy can reduce the expression of Th2 cytokines and increase the expression of Th1 cytokines. This study supports these findings, suggesting that Shenmai injection can further modulate the immune response in patients undergoing chemotherapy for advanced NSCLC.

This study also found that combining Shenmai injection with chemotherapy further shifted the Th1/Th2 balance toward Th1 dominance, thereby enhancing the body's antitumor immunity. Additionally, the combination of Shenmai injection with chemotherapy in patients with advanced tumors appeared to mitigate the myelosuppressive effects of chemotherapy drugs, providing a potential benefit in preserving the patient's immune function.

The results showed that after two cycles of chemotherapy for advanced lung cancer, the levels of IFN-γ and IL-2 were significantly higher in the Shenmai injection group compared to the chemotherapy-only group ($P < .05$). These findings suggest that combining Shenmai injection with chemotherapy can further reverse the shift from Th1 to Th2 cytokine dominance, thereby enhancing the body's antitumor immune response.

Study Limitations

The study has several limitations, including a relatively small sample size and the absence of long-term follow-up data to evaluate the sustainability of the observed immunomodulatory effects. Furthermore, the direct impact of the Shenmai-chemotherapy combination on clinical outcomes such as tumor response, progression-free survival, and overall survival was not assessed. Further large-scale, randomized controlled trials with extended follow-up periods are needed to evaluate the clinical benefits of this combination therapy comprehensively.

CONCLUSION

In conclusion, the combination of Shenmai injection with chemotherapy significantly enhances immune function by modulating T-lymphocyte subsets and cytokine profiles in patients with advanced NSCLC. This improvement in immune parameters suggests a potential role for Shenmai in enhancing antitumor activity. Tracking these immune alterations presents a valuable approach to evaluating the clinical effectiveness of combining therapies, facilitating the identification of optimal chemotherapy protocols for individuals with advanced NSCLC.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

ACKNOWLEDGEMENT

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AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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