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Original Research Article

Efficacy of combined PD-1 immune therapy and chemotherapy in the treatment of locally advanced non-small cell lung cancer

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Abstract

Purpose: *To investigate the clinical efficacy of anti-programmed cell death-1 (PD-1) immunotherapy in combination with chemotherapy in patients suffering from locally advanced non-small cell lung cancer (NSCLC).*

Methods: *A total of 110 NSCLC patients admitted in The Second Affiliated Hospital of Hainan Medical University, Haikou, China were randomly divided into two groups using envelope method. The control group was administered pemetrexed and cisplatin, and the study group was further treated with nivolumab. Each treatment cycle lasted for 21 days, and a total of 6 cycles were administered for the duration of therapy. The short-term objective response rate, adverse reactions, programmed cell death-5 (PDCD-5), tumor necrosis factor-α (TNF-α), tumor necrosis factor-β1 (TGF-β1), and immune status indices were determined.*

Results: *The objective remission rate in study group was 79.25 % (42/53), which was higher than that in control group (61.40 %, 35/57; $p < 0.05$). After treatment, both groups showed higher levels of PDCD-5 and TNF-α compared to their pre-treatment values, while demonstrating lower levels of TGF-β1. Furthermore, PDCD-5 and TNF-α in study group were higher than those in control group, while TGF-β1 was lower than that in control group ($p < 0.05$). In control group, the values of clusters of differentiation 3+(CD3+), 4+(CD4+), and 8+(CD8+) decreased after treatment, while the values of CD8+ increased after treatment. The CD3+, CD4+, and CD4+/CD8+ in study group were higher than those in control group, while CD8+ was lower than those in control group ($p < 0.05$).*

Conclusion: *Anti-PD-1 immunotherapy combination with chemotherapy in the treatment of local NSCLC stabilizes the immune system and improves the short-term efficacy of patients with advanced NSCLC. Further clinical trials are, however, required prior to application of this combination clinical practice.*

Keywords: *Programmed cell death-1, Chemotherapy, Non-small cell lung cancer, Late stage, Curative effect, Immune state*

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INTRODUCTION

Non-small cell lung cancer (NSCLC) is a lung malignant tumor originating from bronchial mucosa, glands, and alveolar epithelium, accounting for most lung cancer types [1,2]. The occurrence of non-small cell lung cancer (NSCLC) is caused by carcinogens in the body

that are not metabolized by enzymes. This leads to genetic mutations in the body, which cannot be repaired promptly by the DNA repair system. As a result, proliferation signals are abnormally enhanced, or apoptotic signals are decreased, leading to the proliferation of cancer cells. Since NSCLC does not show specificity in its early stages, most patients seek medical attention when the disease has already progressed to the middle or late stage, delaying the optimal timing for surgical treatment [3]. Currently, chemotherapy is the main treatment for most NSCLC patients, but a small number of patients develop resistance to chemotherapeutic agents and need to change chemotherapy or combine them with other treatments.

In recent years, immunotherapy has become a new way to treat NSCLC. The blocking therapy of programmed death-1 (PD-1) restores the immune response ability of anti-tumor T cells and also enhances the immune system of individuals diagnosed with advanced NSCLC [4,5]. There is relatively little research on the combination of anti-PD-1 immunotherapy and chemotherapy for the treatment of locally advanced non-small cell lung cancer (NSCLC). This study thus seeks to examine the effectiveness and mode of action of combining chemotherapy with anti-PD-1 immunotherapy for treating patients with NSCLC.

METHODS

Patients

A total of 110 individuals diagnosed with local NSCLC and who were hospitalized at The Second Affiliated Hospital of Hainan Medical University, Haikou, China between December 2019 and January 2020 were chosen as participants in this study. The patients were randomly divided into two groups, with 57 in control group and 53 in study group. The research protocol was approved by The Second Affiliated Hospital of Hainan Medical University Ethics Committee (approval no. HN20191105) and the study followed the guidelines of the Declaration of Helsinki [6].

Inclusion criteria

Patients with confirmed diagnosis through pathological histology and/or cytology examination, aged between 18 and 75 years old, absence of EGFR/ALK mutations, clinical staging of IIIA or IIIB, ECOG score of 0 – 1, KPS score greater than 60, and signed informed consent from either the patient or their family were included in this study.

Exclusion criteria

Patients with acute cardiovascular disease, allergic to the drug components used in the study, impaired liver or kidney function, unwillingness to take contraceptive measures, human immunodeficiency virus (HIV) positive, comorbid psychiatric disorders, prior receipt of other anti-tumor treatments, pregnant or lactating patients and unmeasurable lesions were excluded from the study.

Treatments

For the control group patients, a chemotherapy regimen of pemetrexed and cisplatin was administered, with pemetrexed (manufactured by Dezhou De Pharmaceutical Co., Ltd., NMPA approval number H20080230, specification: 0.5 g/vial) at a dose of 500 mg/m^2 given intravenously over a period of at least 10 min. Thirty minutes after the end of the dose, cisplatin (Jiangsu Haoshen Pharmaceutical Group Co., Ltd., State Drug Administration H20040813, specification: 6 mL: 30 mg) at a dose of 75 mg/m^2, was administered via intravenous drip infusion for at least 2 h. Adequate hydration therapy was given to patients before or after the use of this medication. Each treatment course lasted for 21 days, with a total of 6 courses administered. The treatment group received a combination therapy with PD-1 blockade, in addition to intravenous infusion of the nivolumab monoclonal antibody (manufacturer: Concord Medical International, imported drug registration number: S20180014, specification: 10 mg/mL) at a dose of 3 mg/kg, administered as a continuous infusion for over 1 h. The treatment course was consistent with that of control group. The treatment course was the same as that of control group.

Efficacy criteria

Therapeutic evaluation standards have been established based on the RECIST criteria [7]. These standards include complete response, which is defined as the disappearance of lesions that must be maintained for a period of four weeks. Partial response is defined as a 30 % reduction in the sum of the longest diameters, also maintained for a period of four weeks. Progression is defined as a 20 % increase in the sum of the longest diameters, while stable disease falls between partial response and progression. The objective response rate is calculated as the sum of the complete response rate and the partial response rate.

Determination of PDCD-5, TNF-α, and TGF-β1 levels

Before and after treatment, 5 mL of fasting venous blood from patients was drawn into a vacuum tube, placed in a centrifuge at 3000 rpm, a radius of 10cm, and centrifuged for 5 min. After separating the serum, PDCD-5, TNF-α, and TGF-β1 levels in the serum were determined by enzyme-linked immunosorbent assay (ELISA) using a Muliskan FC ELISA analyzer and reagent kit produced by the American company Thermo Fisher Scientific.

Immunoassay

Before and after treatment, the serum levels of CD3+, CD4+, CD8+, and CD4+/CD8+ were determined using flow cytometry.

Toxic effects

The criteria for toxic effects were based on the International System for the Evaluation of Adverse Reactions to Oncological Drugs, such as proteinuria, hematuria, anemia, and elevated transaminases.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 26.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. Metric data, including PDCD-5, TNF-α, and TGF-β1, were analyzed using K-S test and described using mean ± standard deviations (SD) as appropriate. Statistical comparisons were made using *t*-tests. Count data, such as lesion location and pathological type, were described using percentages and compared using chi-squared test with a four-fold table. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

General data

There were no significant differences in clinical stage, lesion location, pathological type, age, and gender of patients between the two groups ($p > 0.05$, Table 1).

Short-term efficacy

The objective remission rate in study group was 79.25 % (42/53), which was significantly higher than that in control group (61.40 % (35/57) ($p < 0.05$) as shown in Table 2.

PDCD-5, TNF-α and TGF-β1

There were no significant differences in PDCD-5, TNF-α, and TGF-β1 amid the two factions prior to medication ($p > 0.05$, Table 3). After treatment, the values of PDC-5 and TNF-α in both groups were higher than pre-treatment, while the values of TGF-β1 were lower than pre-treatment. After treatment, pdC-5 and TNF-α in study group were higher than those in control group, while TGF-β1 was lower than that in control group ($p < 0.05$).

Table 1: Patients' general data

General information	Control group (n = 57)	Study group (n = 53)	χ^2/t	*P*-value
Gender (n (%))				
Male	30 (52.63)	29 (54.72)	0.048	0.827
Female	27 (47.37)	24 (45.28)		
Mean age (years)	57.25±10.65	58.02±9.71	0.395	0.693
Pathological type (n (%))				
Adenocarcinoma	30 (52.63)	28 (52.83)	1.620	0.445
Squamous cell carcinoma	16 (28.07)	20 (37.74)		
Others	9 (15.79)	5 (9.43)		
Clinical stage (n (%))				
IIIA phase	26 (45.61)	23 (43.40)	0.055	0.815
IIIB stage	31 (54.39)	30 (56.60)		
Location of lesion (n (%))				
Lower right lobe	17 (29.82)	16 (30.19)		
Right superior lobe	15 (26.84)	12 (22.64)	0.219	0.975
Lower left lobe	12 (21.05)	12 (22.64)		
Left superior lobe	13 (22.81)	13 (24.53)		

Table 2: Comparison of short-term efficacy between the two groups (n (%))

Group	N	Complete remission	Partial remission	Steadiness	Advancements	Objective response rate
Control	57	8 (14.04)	27 (47.37)	15 (26.32)	7 (12.28)	35 (61.40)
Study	53	13 (24.53)	29 (54.72)	9 (16.98)	2 (3.78)	42 (79.25)
χ^2						4.163
P-value						0.041

Table 3: Comparison of PDCD-5, TNF-α and TGF-β1 between the two groups (mean ± SD)

Group	N	Pdcd-5 (ng/mL)		TNF-α (pg/mL)		TGF-β1 (ng/mL)	
		Pre-treatment	*Post-treatment*	*Pre-treatment*	*Post-treatment*	*Pre-treatment*	*Post-treatment*
Control	57	0.67±0.12	0.82±0.15*	52.03±4.56	63.77±5.03*	47.56±5.02	35.66±3.74*
Study	53	0.65±0.14	1.03±0.17*	50.74±5.13	76.33±6.74*	49.01±4.78	29.41±3.15*
t		0.207	6.993	1.419	11.275	1.579	9.650
P-value		0.415	0.000	0.159	0.000	0.117	0.000

*$p < 0.05$ Compared with the control group

Immune status

There was no statistical difference in immune status indices between the two groups before treatment ($p > 0.05$). In the control group, the CD3+, CD4+, and CD4+/CD8+ values declined following the intervention, while the values of CD8+ increased after treatment. The immune status indices of the study group did not differ statistically from those pre-treatments ($p > 0.05$). CD3+, CD4+, and CD4+/CD8+ in the study group were higher than those in the control group, while CD8+ was lower than those in the control group ($p < 0.05$) (Table 4).

Adverse reactions

There were no statistical differences in the incidence of gastrointestinal reactions (nausea, vomiting, anorexia), proteinuria, hematuria, decreased WBC, anemia, elevated aminotransferase, and other adverse reactions between the two groups ($p > 0.05$) (Table 5).

DISCUSSION

At present, there is a breakthrough in immunotherapy providing more precise and individualized treatment for patients with NSCLC. Immune checkpoint inhibitors also offer a fresh path for managing patients with lung cancer [8,9]. The PD-1 is expressed in T lymphocytes, monocytes, mesenchymal stem cells, and other cells. The primary ligand of PD-1 (PD-L1) is expressed in tumor cells. The combination of PD-L1 on the surface of tumor cells and PD-1 on the surface of immune cells transmit immunosuppressive signals and inhibit immune function of the body against tumor [10].

Table 4: Comparison of immune status between the two groups (mean ± SD)

Group	N	CD3+		CD4+		CD8+		CD4+/CD8+	
		Pre-treatment	*Post-treatment*	*Pre-treatment*	*Post-treatment*	*Pre-treatment*	*Post-treatment*	*Pre-treatment*	*Post-treatment*
Control	57	57.22±5.14	52.77±5.03*	34.22±4.56	31.44±3.26*	28.25±3.45	30.52±3.77*	1.23±0.23	1.03±0.21*
Study	53	56.63±6.02	58.69±5.41	35.01±4.47	34.89±5.02	27.98±3.69	28.56±4.01	1.25±0.21	1.24±0.27
t		0.563	6.050	0.934	4.352	0.404	2.689	0.485	4.635
P-value		0.575	0.000	0.352	0.000	0.687	0.008	0.629	0.000

**P* < 0.05, Compared with the control group

Table 5: Comparison of adverse reactions between the two groups (n (%))

Group	N	Gastrointestinal reaction	Proteinuria	Hematuria	WBC reduction	Anaemia	Elevated transaminases
Control	57	19 (33.33)	3 (5.26)	5 (8.77)	11 (19.30)	10 (17.54)	7 (12.28)
Study	53	20 (37.74)	4 (7.55)	3 (5.66)	10 (18.87)	8 (15.09)	9 (16.98)
χ^2		0.233	0.240	0.394	0.003	0.120	0.488
P-value		0.630	0.624	0.530	0.954	0.729	0.485

Pemetrexed is a multi-target folic acid antagonist that is utilized in conjunction with cisplatin to enhance clinical manifestations in patients who are suffering from locally advanced non-small cell lung cancer, while Nivolumab is a commonly used clinical PD-1 inhibitor which blocks PD-1/PD-L1 pathway, destroys immunosuppression of tumor cells, and thus play a role in inhibiting tumor growth [11,12]. In this study, the efficacy between two treatment measures and the objective remission rate of the study group was significantly higher than that of control group, indicating that nivolumab combined with anti-PD-1 immunotherapy had significant clinical efficacy for NSCLC patients. Pemetrexed combined with cisplatin efficiently disrupts the typical metabolism of folic acid in cells, thereby hindering the proliferation and expansion of cancerous cells, while avoiding exacerbation of drug-related side effects. In addition, nivolumab reduces the anti-tumor immune response mediated by PD-1 by binding to PD-1 receptor, therefore inhibiting the growth of tumor cells. It has been reported that chemotherapy is the main treatment for locally advanced NSCLC patients, and nearly 4 % of patients that were assisted using anti-PD-1 immunotherapy achieved complete pathological remission [13].

After treatment, PDC-5 and TNF-α levels in the two groups were higher than pre-treatment, while the levels of TGF-β1 were lower than before treatment, and the changes observed in study group were more pronounced than those in control group, indicating that the increased levels of PDC-5 and TNF-α and the decreased levels of TGF-β1 after immunotherapy were important factors for disease control in NSCLC patients with anti-PD-1 therapy. An analysis of its causes showed that PDCD-5 is one of the important members of programmed cell death opal group, which does not directly participate in apoptosis, but acts as an enhancer of apoptosis in order to induce the expression of apoptotic factors.

Anti-PD-1 immunotherapy combined with chemotherapy improves the PDCD-5 level and enhances the expressions of apoptotic factors, so as to achieve the goal of apoptosis of cancer cells [14]. Related studies have shown that PDCD-5 improves the sensitivity and apoptosis of cancer cells, and inhibits their proliferation [15]. Secondly, in patients who respond to immunotherapy, tumor lymphocytes, macrophages, and other cells in the body are activated by PD-1 inhibitors, which disrupt immune suppression and release large amounts of cytokines, including TNF-α. The TNF-α binds to tumor necrosis factor receptors on the surface of its target cells and activates death domains, thereby killing tumor cells, while TGF-β1 is a peptide growth factor that regulates cell proliferation and differentiation and also affects apoptosis and immune system.

The TGF-β1 is a type of polypeptide growth factor, which regulates cell proliferation and differentiation, and also affects cell apoptosis and immune system. Researchers have found that TGF-β1 levels are higher in NSCLC patients compared to other patients. It is believed that the mechanism behind this is that cancer cells damage endothelial cells, causing TGF-β1 to leak into the bloodstream, which in turn leads to an increase in TGF-β1 levels [16,17]. In this study, the TGF-β1 levels in study group were lower than in control group after treatment, indicating that anti-PD-1 immunotherapy combined with chemotherapy can effectively repair endothelial cell damage.

A comparison of immune status indicators between the two groups revealed that CD3+, CD4+, and CD4+/CD8+ in study group were higher than those in control group after treatment, while CD8+ was lower than those in control group, indicating that combined treatment effectively improves the immune status of NSCLC patients, and enhances body resistance. PD-1 is present on T lymphocytes' surface, and once activated, its ligand PD-L1 acts as an inhibitory costimulatory molecule that can hinder the activation of T lymphocytes [18]. T lymphocyte subsets play a crucial role in maintaining a stable immune system in the human body. In patients with non-small cell lung cancer (NSCLC), anti-tumor activity in the body is suppressed, leading to a decrease in CD3+ and CD4+ levels, followed by a decrease in CD4+/CD8+ ratio. This negatively regulates immune response in the body, thereby promoting the proliferation and metastasis of tumor cells [19]. Nivolumab, as a PD-1 inhibitor, restores immune activity of T cells by inhibiting PD-1, improving the immune status of the body, and effectively killing tumor cells [20,21].

Limitations of this study

While the study provides promising results regarding the combination of anti-PD-1 immunotherapy and chemotherapy for the treatment of locally advanced NSCLC, there are some limitations to consider. Firstly, the study only focused on short-term objective response rates and did not evaluate long-term outcomes such as progression-free survival or overall survival. Additionally, the study only included a

small sample size of 110 patients, which may not be representative of the larger population with NSCLC. Moreover, the study only included patients with locally advanced NSCLC, and the results may not apply to patients with different stages of the disease. Finally, the study only examined the efficacy and safety of the treatment combination and did not explore the cost-effectiveness of this treatment compared to other available therapies.

CONCLUSION

Anti-PD-1 immunotherapy combination with chemotherapy in the treatment of local NSCLC stabilizes immune state and improves the short-term efficacy of patients with advanced NSCLC. These findings have the potential to inform clinical practice and guide treatment decisions for patients with advanced NSCLC. Further research is needed to validate these results and explore the long-term efficacy and safety of this combined treatment approach.

DECLARATIONS

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Ethical approval

This study was approved by The Second Affiliated Hospital of Hainan Medical University Ethics Committee, China (approval no. HN20191105).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Yongjie Li and Dunzhi Fu contributed equally to this work.

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