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Original Article

Efficacy of immune checkpoint inhibitors along with chemotherapy in non-small cell lung cancer and the impact on adverse reactions and serum tumor markers

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Abstract: Objective: To examine the efficacy of immune checkpoint inhibitors along with chemotherapy in non-small cell lung cancer (NSCLC) and the effect on adverse reactions and serum tumor markers. Methods: Data of 112 NSCLC patients admitted to Geriatric respiratory department, Xi'an International Medical Center Hospital from February 2018 to March 2021 were analyzed retrospectively. Among them, 54 patients treated with concurrent chemotherapy were labeled as the control group (CG), and 58 patients treated with PD-1/PD-L1 inhibitors in addition to chemotherapy were the observation group (OG). The two groups were compared in terms of immune function indexes, therapeutic efficacy, incidence of adverse reactions, 1-year survival rate, serum tumor markers before and after treatment, and independent risk factors affecting patients' prognosis. Results: Compared to the CG, the OG exhibited significantly better therapeutic efficacy. The levels of IgG, IgA and IgM 6 months after treatment were significantly higher in both groups than those before treatment, and the elevations in the OG were more evident than those in the CG, and the OG demonstrated markedly lower Recombinant Cytokeratin Fragment Antigen 21-1 (CYFRA21-1), Carcinoembryonic antigen (CEA) and Carbohydrate antigen 125 (CA125) levels after treatment than the CG did. Between the two groups, there was no significant difference identified in the incidence of adverse reactions, but the OG was observed to have much higher 1-year survival rate. The pathological stage, differentiation and treatment regimen were independent risk factors affecting patients' prognosis. Conclusion: For NSCLC patients, the adoption of PD-1/PD-L1 inhibitors following chemoradiotherapy shows potential in enhancing clinical efficacy, boosting patients' immune function, and improving long-term survival rates, with premising safety profile.

Keywords: Immune checkpoint inhibitors, chemotherapy, non-small cell lung cancer, immune function, prognosis

Introduction

Lung cancer is a malignant tumor possessing the second highest incidence and mortality on a global basis [1]. Non-small cell lung cancer (NSCLC) makes up approximately 85% of all lung cancer cases [2]. Due to inadequate early screening, a majority of patients are diagnosed at an advanced stage, with only 20%-30% considered clinically operable, and about 50% of NSCLC patients diagnosed with distant metastasis face a poor overall prognosis [3, 4]. Platinum-based chemotherapy has long been the preferred and standard therapeutic regimen for advanced NSCLC, but repeated chemotherapy can lead to drug resistance, as well as increasing adverse reactions [5]. Therefore, finding an effective treatment regimen with minimal adverse reactions is beneficial for NSCLC patients.

As clinical research on the tumor immune microenvironment advances, the clinical application of immune checkpoint inhibitors (ICIs)

targeting the PD-1/PD-L1 pathway has emerged and progressively transformed treatment strategies for advanced NSCLC [6, 7]. The *Chinese Society of Clinical Oncology Guidelines in 2021* have included the adoption of PD-1/PD-L1 inhibitors as monotherapy or in combination with platinum-based chemotherapy for first-line treatment of driver gene-negative advanced NSCLC. These treatment approaches have demonstrated promising efficacy in clinical practice [8]. Despite the widespread use of PD-1/PD-L1 inhibitors, it has been observed that only 20% to 30% of patients could benefit from immune monotherapy [9]. Hence, new treatment regimens are urgently needed for improving survival prognosis.

This study assessed the efficacy of combining PD-1/PD-L1 inhibitors with chemotherapy in the treatment of NSCLC by collecting data of 112 NSCLC patients treated between February 2018 and March 2021. The analysis of their outcomes can offer clinical recommendations for managing NSCLC.

Materials and methods

Clinical data

A retrospective analysis was conducted on a total of 112 NSCLC patients admitted to Xi'an International Medical Center Hospital between February 2018 and March 2021. Among them, 54 patients who received chemotherapy alone were included in a control group (CG), and 58 patients who received ICIs in addition to chemotherapy were in an observation group (OG). The inclusion criteria were as follows: (1) patients who were diagnosed with NSCLC according to the criteria established by WHO, and the diagnosis was confirmed through pathological and imaging examinations [10]; (2) patients at TNM stage IIIB or IV; (3) patients with complete case data. Exclusion criteria were applied, including: (1) patients who had previously received immunomodulators; (2) patients with other major systemic diseases; (3) patients who received chemotherapy or radiotherapy prior to surgery; (4) patients with a predicted survival period of less than 6 months; (5) patients with abnormal kidney or liver function; (6) pregnant or lactating women; (7) patients with other concurrent malignancies. Signed informed consent was obtained from all patients before joining the study. The study protocol is in accordance with the principles outlined in Helsinki Declaration and was approved by the Ethics Committee of Xi'an International Medical Center Hospital.

Treatment methods

Patients in the CG were treated with intravenous gemcitabine (Harbin Yuheng Pharmaceutical Co., Ltd., Zhunzi H20063675, daily dose of 1,000 mg/m^2) + cisplatin (Nanjing Pharmaceutical Factory Co., Ltd., Zhunzi H20103216, daily dose of 75 mg/m^2), with a treatment cycle of 20 days and 6 cycles in total. On this basis, the OG was given PD-1/PD-L1 inhibitor (Suzhou Shengdia Biomedical Co., Ltd., S20190027) 200 mg intravenously every 3 weeks for 6 weeks and 6 cycles in total. Any discomfort or adverse reactions were timely reported to the chief physician and corresponding treatment measures were implemented.

Outcome measures

(1) According to the RECIST criteria (Response Evaluation Criteria in Solid Tumors) [11], the treatment efficacy was assessed in both groups. The evaluation categories included complete response (CR), indicating complete disappearance of the tumor lesion, maintained for a minimum of 4 weeks; partial response (PR), indicating a reduction in the sum of the tumor lesion's diameter by over 30%, sustained for a minimum of 4 weeks; stable disease (SD), indicating the sum of the tumor lesion's diameter did not meet the criteria for PR or progressive disease (PD); and progressive disease (PD), indicating an increase in the sum of the tumor lesion's diameter by more than 20% or the appearance of new lesions. The overall response rate (ORR) was calculated as the percentage of CR or PR cases out of the total number of cases, multiplied by 100%. (2) ELISA was used to measure IgG, IgA, and IgM expressions before and after treatment in both groups. (3) The serum levels of Recombinant Cytokeratin Fragment Antigen 21-1 (CYFRA21-1), Carcinoembryonic antigen (CEA) and Carbohydrate antigen 125 (CA125) were observed and compared between the two groups before and after treatment. (4) The occurrence of adverse reactions during hospitalization was documented and compared between the two groups, including rash, fever, fatigue, and gastrointestinal symptoms. (5) The two groups were also compared in terms of 1-year survival and tumor-free survival. Regular follow-up of all

Table 1. General information table [n (%)]

Factor	Observation Group n = 58	Control Group n = 54	t/X^2	P
Sex			0.006	0.938
Male	38 (65.52)	35 (64.81)		
Female	20 (34.48)	19 (35.19)		
Age (years)			0.008	0.927
≤ 61	21 (36.21)	20 (37.04)		
> 61	37 (63.79)	34 (62.96)		
BMI (kg/m^2)			0.001	0.978
≤ 23	27 (46.55)	25 (46.30)		
> 23	31 (53.45)	29 (53.70)		
Smoking history			0.001	0.982
Yes	42 (72.41)	39 (72.22)		
None	16 (27.59)	15 (27.78)		
Clinical phase			0.009	0.922
Stage IIIB	36 (62.04)	34 (62.96)		
Stage IV	22 (37.93)	20 (37.04)		
Pathological type			0.476	0.788
Squamous cell carcinoma	20 (34.48)	21 (38.89)		
Adenocarcinoma	22 (45.83)	21 (38.89)		
Other	16 (27.59)	12 (22.22)		
Tumor location			0.050	0.823
Left lung	31 (53.45)	30 (55.56)		
Right lung	27 (46.55)	24 (44.44)		

BMI: body mass index.

Table 2. Comparison of efficacy [n (%)]

Efficacy	Observation Group n = 58	Control Group n = 54	X^2	P
Complete response	0	0	-	-
Partial response	36 (62.07)	21 (38.89)	-	-
Stable	17 (29.31)	13 (24.07)	-	-
Disease progression	5 (8.62)	20 (37.04)	-	-
Overall response rate	36 (62.07)	21 (38.89)	6.012	0.014

patients was conducted through hospital visits, telephone calls, text messages, and home visits. The follow-up period extended until the date of death or March 31, 2022, whichever came first. (6) Logistic regression analysis was adopted to identify independent risk factors influencing patients' prognosis.

Statistical methods

Data analysis was performed using SPSS 18.0 (IBM), and figures were generated using GraphPad Prism 8. The chi-square test was adopted to analyze categorical data, while Student t-test was applied for intergroup comparisons of continuous variables. Paired t-tests were performed to evaluate changes before and after treatment within groups. Survival analysis was conducted using log-rank analysis, and Kaplan-Meier curves were generated to illustrate the survival rates. Statistical significance was set at $P < 0.05$.

Results

Subjects were comparable regarding sex, age, and smoking history, with no evident differences observed between the two groups ($P > 0.05$, **Table 1**).

Comparison of treatment efficacy

The OG exhibited an evidently higher ORR than the CG did (62.07% vs. 38.89%). See **Table 2**.

Comparison of immune indexes before and after treatment between two groups

There were no marked differences in IgG, IgA, and IgM levels before treatment ($P > 0.05$). After treatment, however, these levels obviously decreased in the CG, while notably elevated in the OG ($P < 0.05$, **Figure 1**).

Comparison of serum tumor markers

Prior to treatment, no evident differences were identified in levels of serum tumor markers between the two groups ($P > 0.05$). However, the levels of CYFRA21-1, CEA, and CA125 decreased in both groups after treatment. Notably, these tumor markers showed significantly lower levels in the OG than in the CG ($P < 0.05$, **Figure 2**).

Comparison of incidence of adverse reactions during treatment

The difference in the incidence of adverse reactions between two groups was insignificant ($P > 0.05$). Furthermore, all adverse reactions were

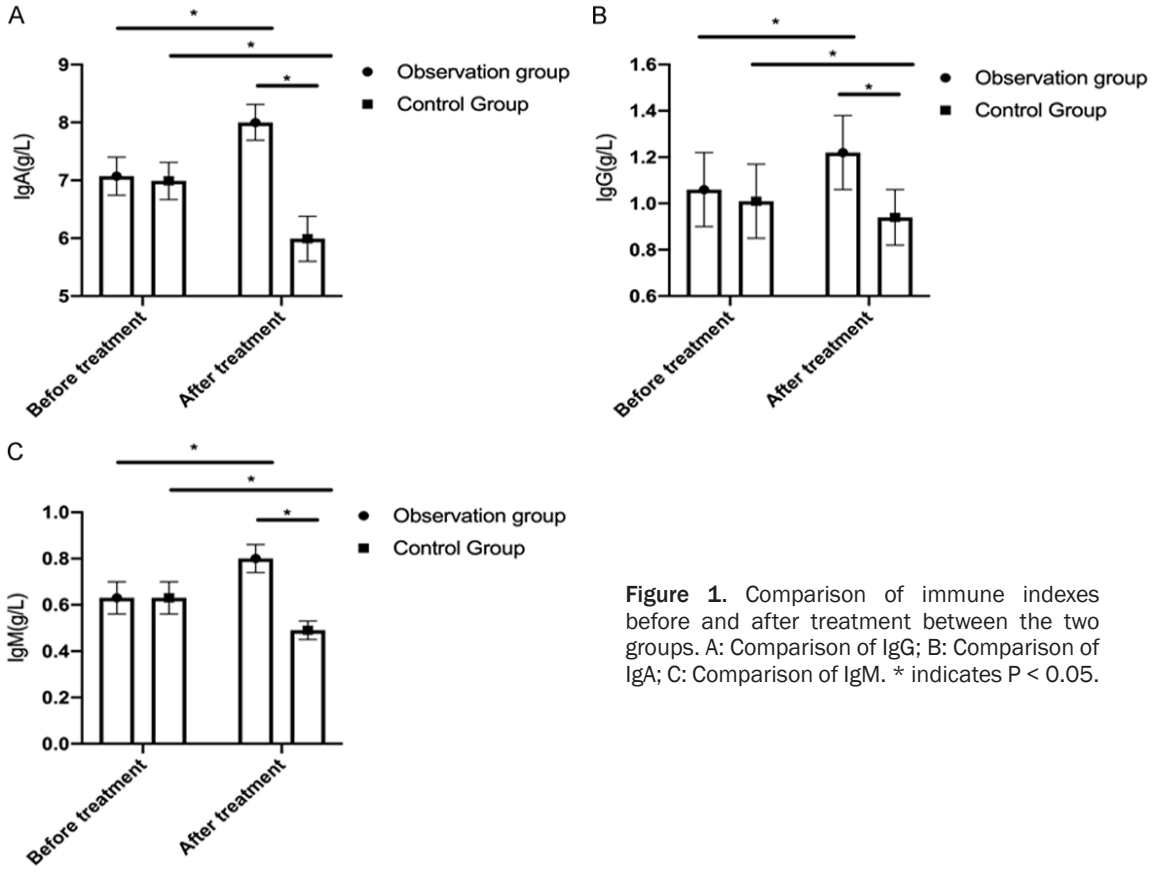

Figure 1. Comparison of immune indexes before and after treatment between the two groups. A: Comparison of IgG; B: Comparison of IgA; C: Comparison of IgM. * indicates $P < 0.05$.

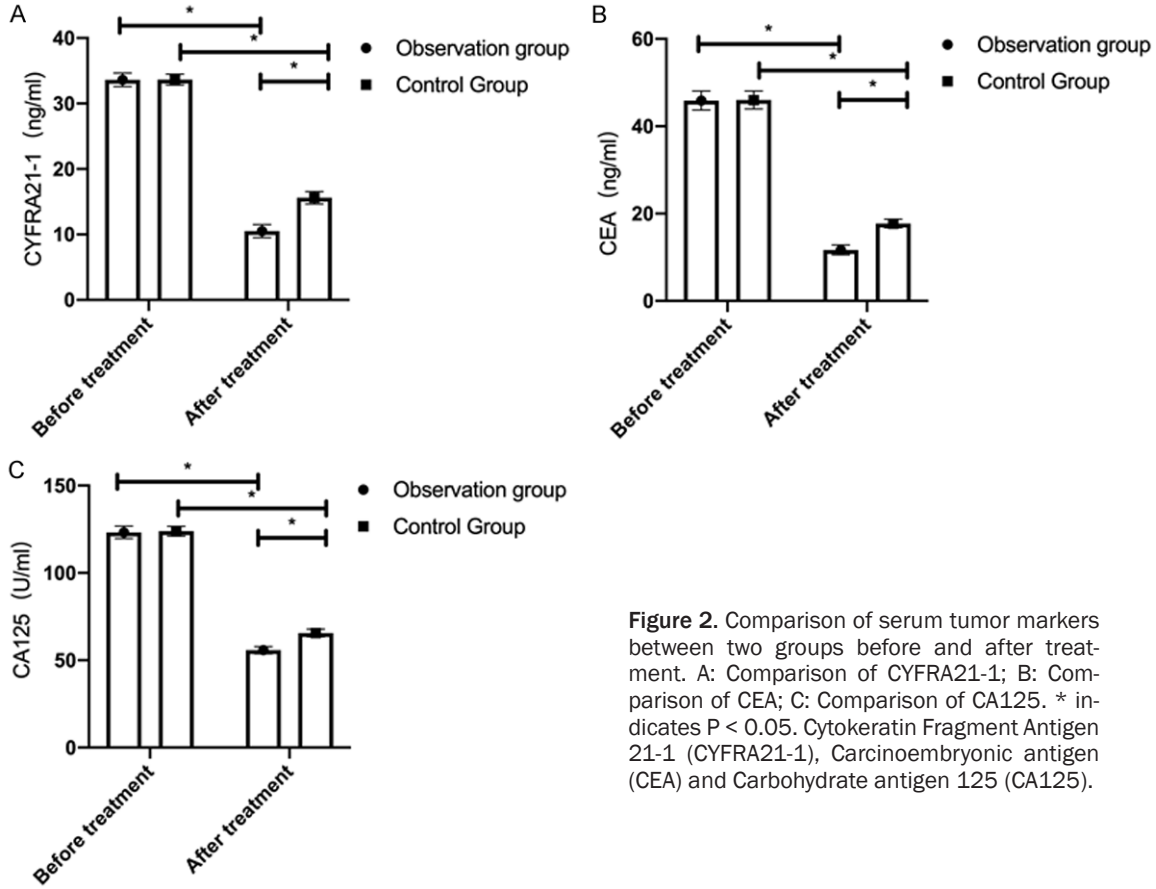

Figure 2. Comparison of serum tumor markers between two groups before and after treatment. A: Comparison of CYFRA21-1; B: Comparison of CEA; C: Comparison of CA125. * indicates $P < 0.05$. Cytokeratin Fragment Antigen 21-1 (CYFRA21-1), Carcinoembryonic antigen (CEA) and Carbohydrate antigen 125 (CA125).

Table 3. Comparison of incidence rate of adverse reactions [n (%)]

Complication	Observation Group n = 58	Control Group n = 54	X^2	P
Rash	3 (5.17)	4 (7.41)	-	-
Fever	2 (3.45)	3 (5.56)	-	-
Fatigue	3 (5.17)	3 (5.56)	-	-
Gastrointestinal symptoms	3 (5.17)	2 (3.70)	-	-
Incidence of adverse reactions	11 (18.97)	12 (22.22)	0.182	0.670

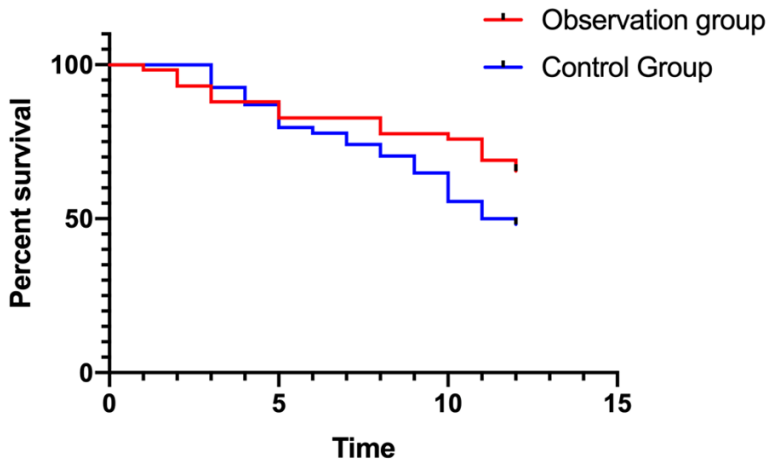

Figure 3. Comparison of 1-year survival rate.

effectively relieved after receiving appropriate symptomatic treatment (**Table 3**).

Comparison of 1-year survival rate between the two groups

The overall survival curve analysis showed that the 1-year survival rate in OG (65.51%, 38/58), was significantly higher than that in CG (48.15%, 26/54) ($P < 0.05$, **Figure 3**).

Analysis of risk factors affecting patient prognosis

Patients were categorized into a death group (n = 57) and a survival group (n = 55) according to their prognosis. Pathological stage, differentiation and treatment regimen were found to be the significant factors affecting their prognosis by univariate analysis (**Table 4**). Further, all these three factors were also determined to be the independent risk factors affecting the prognosis of the patients by logistics regression (**Tables 5**, **6**, $P < 0.05$).

Discussion

While NSCLC is the most common pathological type of primary lung cancer, most patients are already at stage IIIB or IV at the time of diagnosis, with local tumor invasion and distant metastasis depriving them of the chance of surgical treatment, frequently leading to a poor prognosis [12, 13]. In recent years, there has been fundamental progress in cancer treatment, marked by the introduction of novel drugs and diagnostic techniques. These advancements have led to substantial improvements in survival outcomes for patients with malignant tumors. Of particular importance is the advent of immunotherapy, which has revolutionized the treatment approach for NSCLC. Furthermore, with the continuous advancements in molecular biology techniques, an increasing number of molecular targets are being utilized for NSCLC treatment, demonstrating promising therapeutic effects [14]. Research has revealed the significance of immune modulation targeting PD-1/PD-L1 in various domains, such as anti-tumor therapy, combating infections, managing autoimmune diseases, and enhancing the survival of transplanted organs [15]. While the efficacy of ICIs has been established, studies have analyzed the efficacy of ICIs in combination with chemotherapy. However, there is a lack of comprehensive research evaluating the overall impact of ICIs combined with chemotherapy on NSCLC patients. This study not only analyzed the efficacy but also explored tumor markers and adverse reactions associated with it.

In this study, we observed an evidently higher ORR in the OG than that in the CG, indicating that the combination of chemotherapy and PD-1/PD-L1 inhibitors exhibited superior short-term efficacy in treating NSCLC patients, and most of them experienced serious immune

Table 4. Univariate analysis

Factor	Survival Group (n = 55)	Death Group (n = 57)	X^2	P
Sex			0.018	0.892
Male (n = 74)	36 (65.45)	38 (66.67)		
Female (n = 38)	19 (34.55)	19 (33.33)		
Age			0.288	0.591
≤ 61 years old (n = 41)	22 (40.00)	20 (35.09)		
> 61 years old (n = 71)	33 (60.00)	37 (64.91)		
BMI			0.041	0.839
≤ 23 kg/m^2 (n = 52)	25 (45.45)	27 (47.37)		
> 23 kg/m^2 (n = 60)	30 (54.55)	30 (52.63)		
Smoking history			0.009	0.925
yes (n = 81)	40 (72.73)	41 (71.93)		
no (n = 31)	15 (27.27)	16 (28.07)		
Clinical phase			4.823	0.028
Stage III (n = 70)	40 (72.73)	30 (52.63)		
Stage IV (n = 42)	15 (27.27)	27 (47.37)		
Degree of differentiation			7.157	0.008
Low (n = 82)	34 (61.82)	48 (84.21)		
Mid and High (n = 30)	21 (38.18)	9 (15.79)		
Treatment Regimen			6.079	0.014
Chemotherapy alone (n = 54)	20 (36.36)	34 (59.65)		
PD-1/PD-L1 inhibitors combined with chemotherapy (n = 58)	35 (63.64)	23 (40.35)		

BMI: body mass index.

Table 5. Value assignment

Factors	Assignment value
Pathological stage	Stage IV = 1, Stage III = 0
Degree of differentiation	Low = 1, Mid and High = 0
Treatment Regimen	Chemotherapy alone = 1, PD-1/PD-L1 inhibitor combined with chemotherapy = 0

Table 6. Multivariate analysis

Factor	B	S.E,	Wald	P	Exp (B)	95% C.I. of EXP (B)	
						Lower limit	Upper limit
Pathological stage	2.681	0.733	11.696	0.002	12.276	3.145	51.322
Degree of differentiation	1.611	0.673	5.656	0.033	4.863	1.311	18.281
Treatment Regimen	3.223	0.842	14.165	0.001	25.921	5.055	123.311

function inhibition. Among the immunoglobulins present in body fluids, IgG is an antibacterial and antiviral antibody that plays a major role in anti-infective response; IgA contributes to the local immune system, providing protection in collaboration with the surrounding cells; IgM, as a highly efficient antibody, can initiate the early defense mechanisms within the body [16, 17]. Consequently, we conducted a comparative analysis of immune function-related indexes before and after treatment in both groups. The findings revealed that the combination of PD-1/PD-L1 inhibitors with chemotherapy exhibited dual effects: direct cytotoxicity against cancer cells and upregulation of humoral immune markers. This suggests that the combined treatment approach has the potential to restore the tumor cell clearance capability and enhance immune function in patients. In line with this, a previous study [18] reported

that IgG antibodies possessed the ability to bind to Fcγ receptors (FcγRs), thereby triggering antibody-mediated phagocytosis and facilitating complement-based cytotoxicity, which ultimately led to the eradication of tumor cells. In addition, study [19] found that IgG antibodies were closely associated to the prognosis of NSCLC, and NSCLC patients with high IgG antibody levels presented a better prognosis and longer overall survival.

Serum tumor markers, including CA125, CEA and CYFRA21-1, are widely used to assess disease severity and evaluate therapeutic response and prognosis in patients. CYFRA21-1 is a soluble fragment of cytokeratin 19, predominantly found in cancerous breast and lung epithelial cells. It is released into the bloodstream and serves as a tumor marker, particularly for NSCLC detection [20]. CEA, an acid glycoprotein in hollow organs, such as the respiratory and digestive tracts, consists of peptide chains and sugar. It is associated with human embryonic antigenic determinants and found in monocytes, macrophages and multinucleated cells. CEA serves as a specific tumor-associated antigen and has an implication in tumor recurrence [21]. CA125 is a transmembrane glycoprotein containing 5,797 base pairs and expressed in adult tissues of the fetal amniotic membrane, luminal epithelium, as well as luminal epithelium. The concentration of CA125 increases significantly when local malignant transformation or inflammatory stimulation occurs, so it is of great value in the diagnosis and prognosis evaluation of NSCLC [22]. A previous study [23] found that changes in CEA, CA125, and CYFRA21-1 could serve as one of the efficacy evaluation indicators for advanced NSCLC patients undergoing PD-1/PD-L1 inhibitor treatment.

The findings of this study demonstrated that the combination of PD-1 inhibitors and chemotherapy in the treatment of NSCLC effectively reduced the levels of CYFRA21-1, CEA, and CA125 tumor markers. Notably, the combination therapy group (OG) achieved significantly lower levels compared to the chemotherapy alone group (CG). A previous study [24] has also observed similar results to ours, confirming the favorable efficacy of PD-1 inhibitors in treating NSCLC. Moreover, our results exhibited that the incidence of adverse reactions did not significantly differ between the two groups and could be effectively managed by adjusting the drug dosage. This suggests that PD-1/PD-L1 treatment does not substantially increase adverse reactions associated with chemotherapy, indicating good tolerability for NSCLC patients. Furthermore, the survival analysis revealed that patients in the OG exhibited notably higher 1-year overall survival rate compared to those in the CG. Additionally, our analysis identified pathological stage, differentiation, and treatment regimen as independent risk factors influencing patient prognosis.

However, there are still some deficiencies in this study. First of all, due to our small sample size, our conclusions have to be confirmed by further large-sample studies. Secondly, we analyzed humoral immune indicators, which may have the potential to influence immune function. There is a certain deviation in the evaluation, and we will collect more data on cellular immune indicators in the future.

In conclusion, for NSCLC patients, the addition of PD-1/PD-L1 inhibitors to chemotherapy can improve clinical efficacy, enhance immune function, and improve long-term survival rate, with promising safety profile, highlight the significance of considering this combination therapy in clinical practice.

Disclosure of conflict of interest

None.

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