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Original Article

Enhancing safety and therapeutic efficacy: PD-1 inhibitor and recombinant human endostatin combination in advanced non-small cell lung cancer patients

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Abstract: Objective: To assess the therapeutic efficacy of combining a programmed death-1 (PD-1) inhibitor with recombinant human endostatin in patients diagnosed with advanced non-small cell lung cancer (NSCLC). Methods: We retrospectively collected data from 83 patients with advanced NSCLC who received treatment at Xi'an Daxing Hospital between May 2020 and July 2022. Among them, 42 patients were treated with a PD-1 inhibitor combined with recombinant human endostatin (observation group), while 41 patients received PD-1 inhibitor monotherapy (control group). We evaluated the objective response rate, changes in serum tumor markers pre- and post-treatment, occurrence of adverse reactions, progression-free survival (PFS), 1-year survival rate, and identified independent risk factors affecting prognosis in both groups. Results: The treatment efficacy in the observation group significantly surpassed that in the control group. Following treatment, the levels of cytokeratin 19 fragment antigen 21-1, carcinoembryonic antigen, and carbohydrate antigen 125 decreased significantly in the observation group compared to the control group ($P < 0.001$). There was no notable difference in the incidence of adverse reactions between the two groups ($P < 0.001$). The median PFS and 1-year survival rate were notably higher in the observation group ($P < 0.001$). Age, liver metastasis, and treatment regimen emerged as independent risk factors affecting poor prognosis in patients ($P < 0.001$). Conclusion: Combining a PD-1 inhibitor with recombinant human endostatin in patients with advanced NSCLC not only enhances clinical efficacy but also increases PFS and the 1-year survival rate while ensuring treatment safety. This combination therapy shows promise for clinical application.

Keywords: PD-1 inhibitor, recombinant human endostatin, first-line chemotherapy, advanced non-small cell lung cancer

Introduction

Lung cancer remains a prevalent and deadly malignancy in China, posing a significant health burden [1]. Non-small cell lung cancer (NSCLC), encompassing roughly 85% of all lung cancer cases, often lacks noticeable symptoms in its early stages. Consequently, the majority of patients (70% to 80%) are diagnosed at an advanced stage, precluding surgical resection and necessitating systemic pharmacotherapy as the primary treatment option [2, 3].

Recently, immune checkpoint inhibitors have shown promise in cancer immunotherapy. Programmed death-1 (PD-1), a key immune coinhibitory molecule, regulates immune responses to human cells and maintains self-tolerance by dampening T-cell-mediated immunity. As a primary therapeutic target for gene-negative advanced NSCLC, PD-1 inhibition has significantly extended survival benefits for select patients [4-6]. However, immune monotherapy is effective primarily in patients with high PD-1 expression, limiting its application to a broader patient population [7]. Recombinant human endostatin, an antagonist of vascular endothelial growth factor, inhibits tumor angiogenesis through multiple pathways and has shown promising results in treating various solid tumors. Its potential as a combination therapy with immunotherapy is appealing [8]. A recent study compared the clinical efficacy of two immune combination therapies: immunothera-

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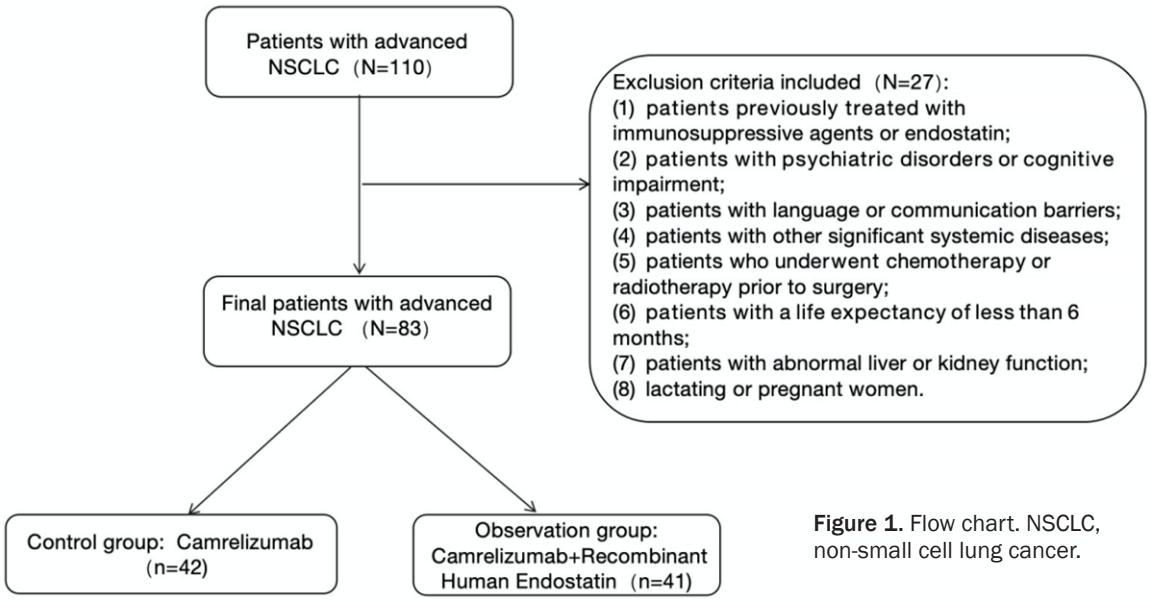

Figure 1. Flow chart. NSCLC, non-small cell lung cancer.

py combined with recombinant human endostatin and immunotherapy combined with chemotherapy, as second-line treatments for advanced NSCLC [9]. The findings suggested that combining immunotherapy with anti-angiogenesis treatment can achieve synergistic effects through diverse mechanisms. However, real-world applications of this approach are still limited in research.

To further evaluate the efficacy and safety of combining immunotherapy with recombinant human endostatin in NSCLC patients, we retrospectively analyzed 83 cases of advanced NSCLC patients treated between May 2020 and July 2022. The aim is to provide additional clinical treatment options for managing advanced NSCLC patients.

Materials and methods

Clinical data

A retrospective analysis was conducted on 83 patients with advanced NSCLC treated at Xi'an Daxing Hospital between May 2020 and July 2022. The patients were divided into two groups: the observation group (42 patients treated with PD-1 inhibitors combined with endostatin) and the control group (41 patients treated with PD-1 inhibitors alone).

The inclusion criteria were as follows: (1) Patients diagnosed with NSCLC according to the diagnostic criteria outlined by the World Health Organization, confirmed by imaging and pathological examination; (2) Patients staged as III B or IV using the TNM classification; (3) Patients with complete medical records; (4) Patients who underwent the specific drug treatment and had post-treatment outcomes evaluated.

The exclusion criteria encompassed: (1) Patients previously treated with immunosuppressive agents or endostatin; (2) Patients with psychiatric or cognitive impairments; (3) Patients with language or communication barriers; (4) Patients with other significant systemic diseases; (5) Patients who underwent chemotherapy or radiotherapy prior to immunotherapy; (6) Patients with a life expectancy of less than 6 months; (7) Patients with abnormal liver or kidney function; (8) Lactating or pregnant women.

This study received approval from the Ethics Committee of Xi'an Daxing Hospital and adhered to the principles outlined in the Helsinki Declaration. A flow chart is provided in **Figure 1**.

Treatment methods

Patients in other groups received gemcitabine (National Medical Products Administration approval number: H20123362; Jiangsu Jerray Pharmaceutical Co., Ltd.; daily dose of 1,000 mg/m^2) plus cisplatin (National Medical Products Administration approval number: H20023461; Qilu Pharmaceutical Co., Ltd.;

daily dose of 75 mg/m^2) for chemotherapy. The treatment cycle was 20 days, with a total of 6 cycles.

The control group received intravenous infusion of the PD-1 inhibitor (Jiangsu Hengrui Pharmaceutical Co., Ltd., national drug approval number: S20190027), with a cycle of 21 days for a total of 6 cycles (Only PD-1 inhibitor was used in this study).

The observation group received recombinant human endostatin (Shandong Simcere Diagnostics Co., Ltd., National Medical Products Administration approval number: S20050088, specification: 15 mg) in addition to the treatment received by the control group. They were administered a fixed dose of 210 mg continuously for 72 hours, with a cycle of 21 days for a total of 3 cycles. Both groups were treated for 3 cycles.

If patients experienced discomfort or adverse reactions, they were instructed to promptly report to a senior physician and take corresponding treatment measures.

Primary outcome measures: (1) One week post-treatment, the objective response rate (ORR) in both patient groups was assessed and compared using the Response Evaluation Criteria in Solid Tumors (RECIST) [10]. ORR includes complete response (CR), characterized by the disappearance of lesions for at least 4 weeks; partial remission (PR), indicated by a minimum 30% reduction in the sum of target lesion diameters for at least 4 weeks without new lesions; stable disease (SD), denoted by insufficient shrinkage for PR or insufficient growth for progressive disease (PD); and PD, marked by at least a 20% increase in the sum of target lesion diameters or the appearance of new lesions. ORR was calculated as (number of CR + number of PR)/total number of cases × 100%. (2) Comparison of Progression-Free Survival (PFS) and overall survival rates at one year was conducted between the two groups.

Secondary outcome measures: (1) One week post-treatment completion, serum tumor marker levels, including cytokeratin 19 fragment antigen 21-1 (CYFRA21-1), carcinoembryonic antigen (CEA), and carbohydrate antigen 125 (CA125), were measured and compared before and after treatment using electrochemiluminescence immunoassay. (2) Treatment safety was assessed according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0) [11], which categorizes adverse events into five grades. (3) Univariate and multivariate analyses were conducted using the Cox proportional hazards model to investigate the association between baseline variables and patient prognosis.

Statistical analysis

This study utilized Excel tables for data collection and organization. Data analysis was conducted using SPSS 18.0 (IBM) software, with graphs generated using GraphPad Prism 8 software. Count data were presented as number of cases (%), and the chi-square test was employed. Measurement data were expressed as mean ± SD. Paired samples t-test was utilized for within-group comparisons before and after, while independent sample t-test was employed for between-group comparisons. Survival analysis was conducted using the log-rank test, and survival curves were plotted using the Kaplan-Meier method. The Cox proportional hazards model was used to analyze the relationship between baseline variables and patient prognosis. A significance level of $P < 0.05$ was considered statistically significant.

Results

Comparison of general data

No significant differences were observed between the two groups regarding gender, age, smoking history, or other baseline characteristics ($P > 0.05$), indicating comparability (**Table 1**).

Comparison of ORR

The ORR in the observation group was 76.19%, significantly higher than that in the control group (45.24%, P=0.004) (**Table 2**).

Comparison of survival

During the follow-up period, tumor progression occurred in 57.14% (24/42) of patients in the observation group and 82.93% (34/41) in the control group. The median PFS time was 11 months in the observation group and 6 months in the control group, demonstrating a significant difference ($P < 0.001$). At the 1-year follow-

Table 1. Comparison of general data [n (%)]

Factor	Observation group (n=42)	Control group (n=41)	t/X^2	P
Gender			0.105	0.747
Male	23 (54.76)	21 (51.22)		
Female	19 (45.24)	20 (48.28)		
Age			0.291	0.590
≤ 65	17 (40.48)	19 (46.34)		
> 65	25 (59.52)	22 (53.66)		
Body mass index (kg/m^2)			0.108	0.743
≤ 23	22 (52.38)	20 (48.78)		
> 23	20 (47.62)	21 (51.22)		
Smoking history			0.186	0.666
Yes	30 (71.43)	31 (75.61)		
No	12 (28.57)	10 (24.39)		
Clinical stage			0.011	0.916
III	22 (52.38)	21 (51.22)		
IV	20 (47.62)	20 (48.78)		
Pathological type			0.115	0.944
Squamous cell carcinoma	15 (35.71)	14 (34.15)		
Adenocarcinoma	20 (47.62)	19 (46.34)		
Other	7 (16.67)	8 (19.51)		
Comorbid diseases			0.056	0.972
Hypertension	20 (47.62)	21 (51.22)		
Diabetes	16 (38.10)	15 (36.59)		
Other	6 (14.29)	6 (14.63)		

Table 2. Comparison of ORR between two groups [n (%)]

Curative effect	Observation group (n=42)	Control group (n=41)	X^2	P
CR	0	0		
PR	22 (52.38)	15 (36.59)		0.148
SD	10 (23.81)	7 (17.07)	2.095	
PD	10 (23.81)	19 (54.76)		
ORR	32 (76.19)	23 (45.24)	8.435	0.004

ORR, Objective Response Rate; CR, Complete Response; PR, Partial Remission; SD, Stable Disease; PD, Progressive Disease.

up, 76.19% (32/42) of patients in the observation group achieved a 1-year survival rate, while 41.46% (17/41) of patients in the control group reached a 1-year survival rate. The 1-year survival rate in the observation group was notably higher than that in the control group, with a statistically significant difference (P < 0.001) (**Figure 2**).

Comparison of serum tumor markers before and after treatment

Before treatment, there were no statistically significant differences in the levels of serum tumor markers between the two groups (P > 0.05). Following treatment, the levels of CYFRA21-1, CEA, and CA125 in both groups decreased compared to their pre-treatment levels. Notably, the levels in the observation group were markedly lower than those in the control group, with statistically significant differences (P < 0.001) (**Figure 3**).

Comparison of treatment-related adverse events (AE) incidence

In the observation group, the proportions of patients experiencing grade 1, grade 2, and

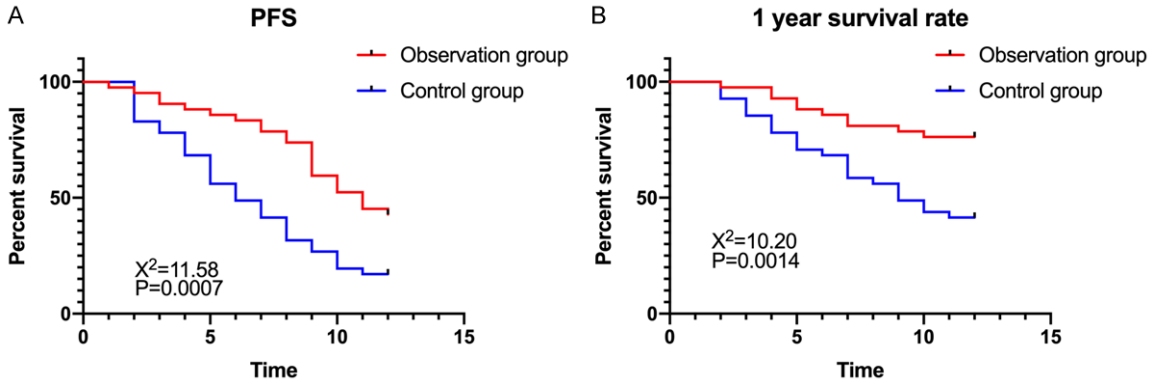

Figure 2. Comparison of survival. A: Comparison of PFS between the two groups of patients; B: Comparison of the 1-year survival rates of the two groups of patients. PFS, progression-free survival.

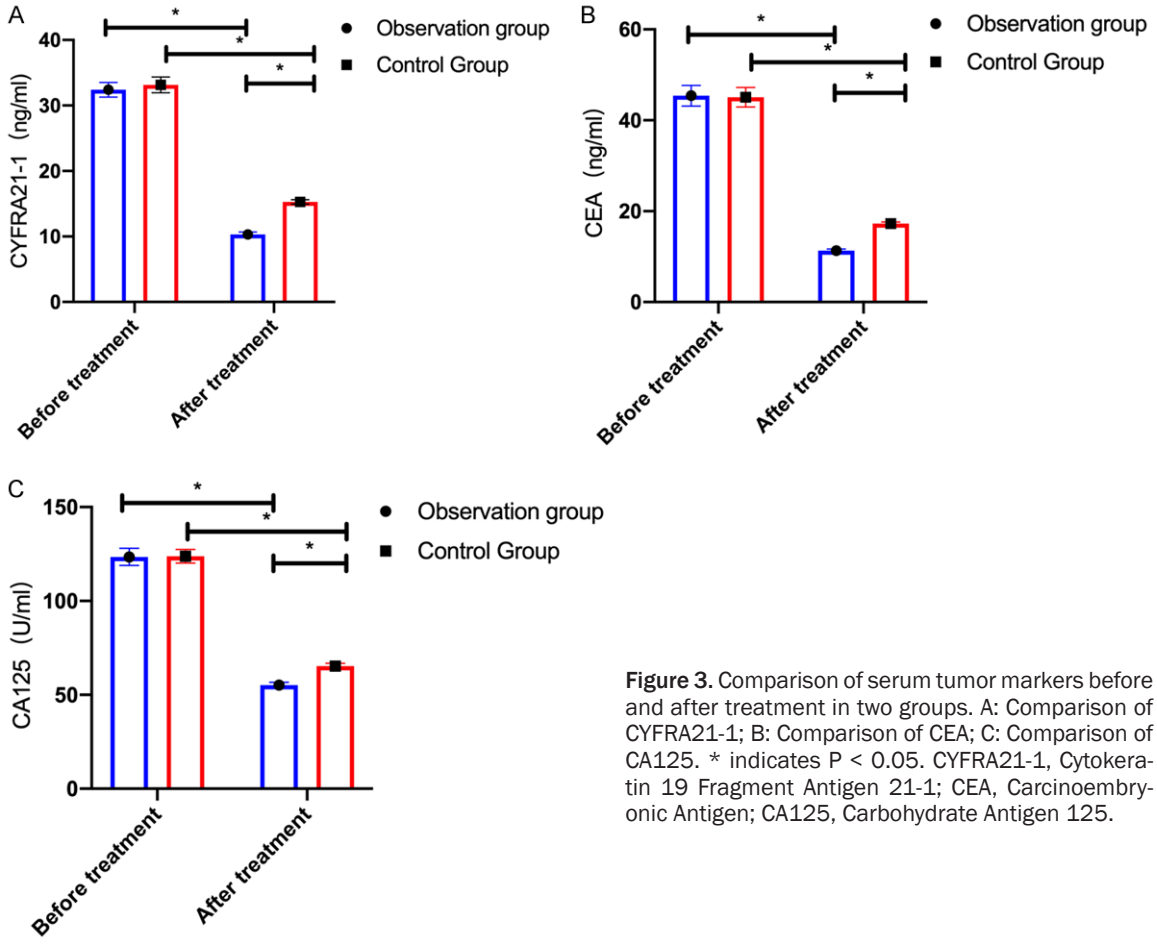

Figure 3. Comparison of serum tumor markers before and after treatment in two groups. A: Comparison of CYFRA21-1; B: Comparison of CEA; C: Comparison of CA125. * indicates $P < 0.05$. CYFRA21-1, Cytokeratin 19 Fragment Antigen 21-1; CEA, Carcinoembryonic Antigen; CA125, Carbohydrate Antigen 125.

grade 3-4 AEs were 47.62%, 23.81%, and 28.57%, respectively. Conversely, in the control group, the proportions were 51.22%, 29.27%, and 19.51%, respectively. There was no significant difference in the incidence of AEs between the two groups ($P > 0.05$) (**Table 3**).

Analysis of factors influencing patient prognosis

To analyze potential risk factors affecting patient survival benefits, we conducted univariate and multivariate Cox proportional hazards

Table 3. Comparison of treatment-related AE incidence

Grading	Observation group (n=42)	Control group (n=41)	X^2	P
1	20 (47.62)	21 (51.22)	0.108	0.743
2	10 (23.81)	12 (29.27)	0.317	0.573
3-4	12 (28.57)	8 (19.51)	0.931	0.335

Table 4. Univariate and multivariate COX regression analysis of factors related to patient prognosis

Factor	Single factor		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Gender	1.15 (0.59~2.13)	0.592	-	-
Male (n=44)				
Female (n=39)				
Age	0.45 (0.32~0.79)	0.001	0.94 (0.932~1.032)	0.029
≤ 65 (n=36)				
> 65 (n=47)				
Body mass index	0.95 (0.55~1.64)	0.751	-	-
≤ 23 kg/m^2 (n=42)				
> 23 kg/m^2 (n=41)				
Smoking history	0.82 (0.57~1.28)	0.419	-	-
Yes (n=61)				
No (n=22)				
Liver metastasis	2.55 (1.11~5.46)	0.028	2.98 (1.03~8.44)	0.033
Yes (n=31)				
No (n=52)				
Treatment programs	0.57 (0.38~0.95)	0.015	0.59 (0.032~0.98)	0.024
Single PD-1 treatment (n=41)				
PD-1 combined with recombinant human endostatin treatment (n=42)				

models with 1-year overall survival achievement (i.e., occurrence of a poor prognosis) as the dependent variable. In the multivariate analysis, age (Hazard Ratio [HR]: 0.94, P=0.029) and liver metastasis (HR: 2.98, P=0.033) were identified as independent adverse prognostic factors. Conversely, treatment with PD-1 combined with recombinant human endostatin was shown to be a protective factor for prognosis in patients (HR: 0.59, P=0.024). See **Table 4**.

Discussion

Lung cancer exhibits a high clinical incidence rate, and is exacerbated by the deteriorating surrounding environment and worsening air pollution in recent years [12]. Currently, chemotherapy remains pivotal in treating NSCLC; however, the occurrence of adverse reactions during chemotherapy cannot be overlooked, often leading some patients to discontinue treatment due to intolerability [13]. Therefore, finding new treatment strategies holds significant clinical importance. PD-1 serves as a vital immune inhibitory molecule, and immune regulation targeting PD-1 plays a crucial role in combating tumors, infections, autoimmune diseases, and promoting the survival of transplanted organs [14].

While PD-1 inhibitors have demonstrated improved tumor remission rates as first- and second-line treatments for NSCLC, a considerable portion of patients still fail to benefit from these approaches alone [15]. Recent years have shown promising results with the combination of immunotherapy and anti-angiogenesis therapy in NSCLC. However, real-world application data still remain scarce. Our study demonstrates a significantly improved total remission rate in the observation group receiving

PD-1 inhibitor combined with recombinant human endostatin therapy compared to the control group treated with PD-1 inhibitors alone. This indicates a superior short-term efficacy for NSCLC patients receiving the combined therapy. Tumor angiogenesis, a critical process in tumor occurrence, growth, and metastasis, involves the recruitment of endothelial cells into the tumor [16, 17]. This aberrant tumor vascular system not only accelerates disease progression but also establishes an immunosuppressive environment by hindering antigen-specific T cell maturation, impeding T cell infiltration, and attracting suppressive cells to the tumor site. Consequently, inhibiting angiogenesis is believed to reshape the tumor immune microenvironment and enhance immunotherapy efficacy [18], which aligns with our findings.

Furthermore, our comparison of median PFS and 1-year overall survival rates between the two groups revealed significantly higher values in the observation group. This suggests that the combined therapy of PD-1 inhibitors and recombinant human endostatin can effectively prolong survival and offer significant survival benefits for NSCLC patients. This outcome can be attributed to the inhibitory effects of recombinant human endostatin on endothelial cell proliferation in tumor neovascularization, promoting atrophy and closure of tumor blood vessels. This action improves tissue interstitial pressure and reduces distant metastasis caused by tumor cells entering the bloodstream. Furthermore, it rectifies the local tumor microenvironment disorder by inducing deactivation of hypoxia response genes like erythropoietin and erythropoietin receptor, exerting anti-angiogenic effects. In combination with immunotherapy, this synergistic action enhances treatment efficacy [19, 20].

Serum tumor markers CYFRA21-1, CEA, and CA125 exhibit a strong correlation with disease progression and prognosis in NSCLC. Elevated levels of these markers often indicate poorer outcomes. CYFRA21-1, a soluble acidic protein of cytokeratin detected using monoclonal antibodies, is particularly valuable in assessing NSCLC status. It is primarily found in the epithelium of breast and lung cancers and its release into the bloodstream is clinically significant in evaluating NSCLC treatment efficacy [21]. CEA, an acidic glycoprotein primarily located on tumor cell surfaces, partly reflects tumor neovascular activity and plays a crucial role in assessing tumor development and metastasis. Overexpression of CEA can inhibit tumor cell death and is negatively associated with the prognosis of stage IV NSCLC [22]. CA125, a tumor-associated glycoprotein abundant in malignant tissues and tumor cells, is released into the blood following tumor tissue destruction, carrying diagnostic and prognostic value for NSCLC [23]. Our study demonstrates a decrease in CYFRA21-1, CEA, and CA125 levels after treatment in both patient groups, with significantly lower levels seen in the observation group compared to the control. This finding suggests that the combination of PD-1 inhibitor and recombinant human endostatin therapy effectively ameliorates NSCLC, exhibiting superior efficacy to PD-1 inhibitor monotherapy. Furthermore, when comparing adverse reactions between the two groups, we primarily observed grades 1-2 reactions with fewer instances of grades 3-4, and no significant difference between the groups. Notably, all adverse reactions were alleviated with appropriate management, indicating that combined therapy does not significantly increase adverse reactions and demonstrates good tolerance among NSCLC patients.

Lastly, our analysis identified age, vascular cancer embolus, and treatment regimen as independent risk factors that significantly influence patient prognosis. This crucial understanding aids in formulating personalized treatment plans tailored to individual patient conditions, ensuring optimal outcomes. However, this study is not without limitations. Firstly, the follow-up duration of one year may be insufficient for comprehensive assessment of long-term survival outcomes. Future studies with extended follow-up periods are necessary to further update and refine overall survival data. Secondly, the relatively small sample size may limit the generalizability of our findings. Therefore, larger-scale studies are warranted to validate our results and establish the broader applicability of this treatment strategy.

In summary, for patients with NSCLC, the combination of PD-1 inhibitors with recombinant human endostatin therapy offers superior

clinical efficacy and survival rates while maintaining treatment safety. Consequently, this approach holds promise for widespread clinical application.

Disclosure of conflict of interest

None.

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