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Original Article

Effectiveness and safety of recombinant human endostatin injection plus immune checkpoint inhibitors for non-small cell lung cancer: a single-centered, retrospective study

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Abstract: To evaluate the clinical effectiveness and safety of recombinant human endostatin (rh-Endo) injection plus immune checkpoint inhibitor (ICI) treatment of non-small cell lung cancer (NSCLC) treatment. We collected the medical records and follow-up data of inoperable NSCLC patients who received the corresponding anti-tumor treatment for at least 4 cycles and were discharged from our hospital from January 2021 to January 2023 for a retrospective analysis. According to the treatment methods, they were assigned to rh-Endo+ICIs (Endostatin+ICIs) and ICIs groups. Rh-Endo injection was administered at 210 mg each time via continuous chemotherapy pump infusion for 3 days, once every 3 weeks. The use of ICIs followed the instructions. Neither rh-Endo injection nor ICIs were allowed to be administered at a reduced dose. Therapeutic efficacy was compared between groups, tumor biomarkers, health status, and life quality were observed, and the occurrence of adverse reactions was documented. Progression-free survival (PFS) and overall survival (OS) during patient follow-up (2 years) were tracked. In this study, 114 eligible cases were included, with 73 receiving ICIs+rh-Endo. The disease control rate (DCR) of the ICIs and Endostatin+ICIs groups was 46.35% and 75.34% (P=0.002), respectively. Both cohorts exhibited reduced serum cytokeratin 19 fragment (CYFRA21-1), squamous cell carcinoma antigen (SCCA), carbohydrate antigen 50 (CA50) after three cycles of treatment, especially in the Endostatin+ICIs group (P<0.05). Endostatin+ICIs also contributed to better health status and life quality in patients compared to ICIs. The Endostatin+ICIs group displayed longer mean PFS (10.6 months vs. 6.8 months) and mean OS (17.6 months vs. 8.3 months) than the ICIs group. The results indicated that rh-Endo injection plus ICIs showesno significantly difference compare to ICIs alone in the adverse reaction rate, shows superior efficacy in improving clinical efficacy, significantly prolonging PFS and OS, and boosting patients' health status and quality of life.

Keywords: Recombinant human endostatin (rh-Endo), immune checkpoint inhibitors (ICIs), non-small cell lung cancer (NSCLC), adverse effects

Introduction

Lung cancer (LC) is among the most common and deadly malignant tumors worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for ~85% of all LC histopathological types, and only 15% live beyond 5 years after diagnosis, presenting a serious situation [2]. Platinum-based chemotherapy was used to be the first-line therapy for advanced NSCLC patients without driver gene mutations, but the treatment outcomes were always less than satisfactory [3, 4]. In the past two decades, remarkable progress has been made in the field of chest oncology, especially in the treatment of NSCLC. This progress spans several aspects, from LC screening to the introduction of innovative treatment programs, including immune checkpoint inhibitors (ICIs) and personalized targeted therapy for oncogene-addicted NSCLC (a single driving mutation necessary for tumor survival) [5, 6].

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The significant breakthrough in ICI therapy has made it a better option for treating patients with advanced NSCLC [7]. Tumor immunotherapy involves activating the immune cells in the body to enhance the anti-tumor immune response, specifically eliminating small residual tumors and inhibiting tumor growth, thereby breaking immune tolerance [8]. Among the immunotherapy drugs, the most prominent ones are the programmed death receptor 1 (Programmed Death 1, PD-1) and programmed death ligand 1 (PD-L1) inhibitors. By inhibiting the interaction between PD-L1/PD-L2 on tumor cell surfaces and PD-1 on T lymphocyte surfaces, PD-1/PD-L1 inhibitors can effectively activate the immune system, enabling it to launch a destructive attack against tumor cells [9, 10]. In addition, recombinant human endostatin (rh-Endo) injection has been proven to bind with signal molecules like integrins and vascular endothelial growth factor (VEGF) receptor (VEGFR) to suppress phosphorylation caused by VEGF, thus preventing VEGF-induced downstream signal cascade of FAK/Ras/Raf/ERK/MAPK and playing a role in inhibiting tumor angiogenesis [11]. Many clinical trials show that rh-Endo injection combined with chemotherapy can improve the first-line treatment effect of NSCLC without increasing toxicity; however, the efficacy of rh-Endo injection as a monotherapy is limited [12, 13]. Meanwhile, there are patients inherently resistant to ICIs as well as cases developing acquired resistance after treatment, meaning that the population benefiting from ICIs monotherapy is considerably limited [14]. By adopting a combined treatment approach, it is expected to increase the proportion of patients responding to ICI therapy, which can be regarded as a feasible strategy. Antiangiogenic drugs and ICIs have a synergistic effect in anti-tumor therapy [15-18]. Bevacizumab combined with atezolizumab is superior to atezolizumab in the treatment of advanced NSCLC [19]. However, there are currently few domestic reports on the use of rh-Endo combined with ICIs for advanced NSCLC. Over decades, tumor angiogenesis has been substantially demonstrated to be inevitable in solid tumours' malignant phenotypes (growth, proliferation, metastasis, etc.) [20, 21]. Anti-angiogenic agents contribute to effective existing tumor vasculature degrading, bloked tumor angiogenesis, enhanced immune cell infiltration within the tumor milieu, alleviated immunosuppression, and positively modulated immune function [22, 23]. Furthermore, ICIs can amplify the efficacy of anti-angiogenic agents by promoting vascular remodeling. In view of this, this study selected patients with advanced NSCLC seeking treatment at the hospital, aiming at providing some scientific basis for improving patient prognosis and enhancing treatment efficacy.

Information and methodology

Research population

The medical and follow-up data of non-resectable NSCLC patients who received corresponding anti-tumor treatment for at least 4 cycles in Shanxi Hospital Affiliated to Cancer Hospital (January 2021-January 2023) were retrieved for a retrospective analysis. Patient eligibility: (1) NSCLC diagnosed by histology or cytology; (2) The absence of targeted gene mutations (e.g., EGFR, C-ros oncogene 1 receptor tyrosine kinase [ROS1], anaplastic lymphoma kinase [ALK]) confirmed by driver mutation testing in non-squamous NSCLC cases; (3) TNM stage: IIIb-IV; (4) Karnofsky score (KPS) >60; (5) Normal organ function and cardiac function; (6) Measurable lesion ≥1; (7) Expected survival patients 3 months; (8) Treatment with the corresponding therapeutic regimen for at least 4 cycles; (9) Complete clinical medical records and follow-up data. Exclusion grounds: (1) Malignant tumors of other systems (except carcinoma in situ) within 5 years before/after LC treatment; (2) Prior use of standard chemoradiotherapy, anti-angiogenic drugs, or ICIs before enrollment; (3) Seriously allergies to ICIs; (4) Active bleeding or bleeding risk; (5) White blood cell count $<2\times10^9$/L, neutrophil count $<1\times10^9$/L or platelet count $<50\times10^9$/L; (6) Being mentally ill and unable to communicate effectively; (7) Defective clinical data. Ethical approval has been secured from the Medical Ethics Committee of Shanxi Province Cancer Hospital. See **Figure 1** for the patient selection flowchart.

Patient data collection

Reviewing patients' electronic medical records, we gathered their general clinical data, including gender, age, pathological type, ECOG stage, smoking history, tumor stage, KPS score, metastatic site, and type of immunotherapy agent.

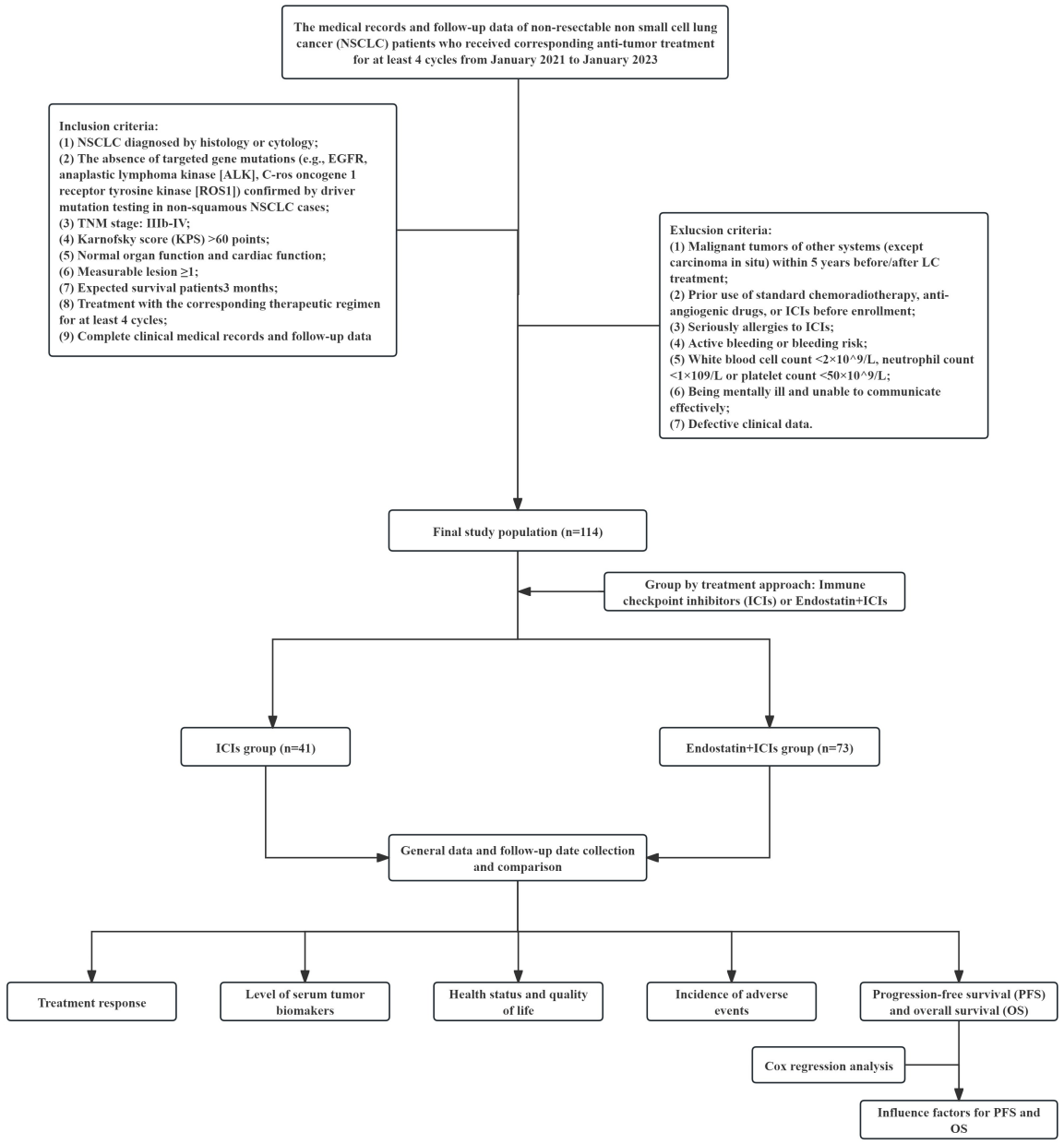

Figure 1. The flow chart of the study.

Biochemical indicators included pre- and post-treatment tumor marker levels. The primary endpoints comprised progression-free survival (PFS) and overall survival (OS), with objective response rate (ORR), disease control rate (DCR), and clinical safety being secondary.

Treatment methods

Patients were allocated to an Endostatin+ICIs group (treated with rh-Endo and ICIs) and an ICIs group (managed with ICIs alone) according to the treatment methods. Rh-Endo Injection was ordered from Shandong Simcere-Medgenn Bio-pharmaceutical Co., Ltd., with the specification of 15 mg/2.4×10^5 U/3 ml/vial, and the SFDA Approval Number of S20050088. The dosage was 210 mg, administered by continuous intravenous infusion for 72 hours, once every 3 weeks. ICIs included Camrelizumab (Jiangsu Hengrui Pharmaceuticals Co., Ltd.), Sintilimab (Innovent Biologics (Suzhou) Co., Ltd.), Pembrolizumab (Zhengda Tianqing Kangfang (Shanghai) Biopharmaceu-

tical Technology Co., Ltd.), and Tislelizumab (BeOne Medicines Ltd.). The medication was administered by intravenous drip at a dose of 200 mg every three weeks [24-27]. Patients receiving ICIs were treated with PD-1/PD-L1 inhibitors, specifically those with PD-L1-positive or high expression. The specific choice of therapy was incorporated a comprehensive assessment of the patient's lung cancer subtype, stage, and genetic testing results.

Endpoints

Curative effects: Imaging examinations were performed before the first administration to understand the patient's baseline condition, including whole body PET/CT or chest contrast-enhanced CT, head and upper abdomen contrast-enhanced CT/MR, and whole body bone scan. Based on the RECIST assessment, the tumor response was evaluated after every 2-3 treatment cycles regarding the patient's short-term prognosis. No new lesion occurrence for at least one month, plus complete elimination of the original tumor lesion, is considered complete remission (CR). The partial remission (PR) criterion is a >30% reduction in the sum of the tumor maximal diameter (TMD) and maximal vertical diameter; if the sum of the TMD and the maximum vertical diameter increases by less than 20%, it is recorded as a stable disease (SD); progressive disease (PD) is defined as new lesion appearance or an increase of ≥20% in the sum of TMD and maximal vertical diameter. Objective remission rate (ORR) = CR rate+PR rate; disease control rate (DCR) = PR rate+SD rate+CR rate.

Tumor markers and inflammatory indicators: Before treatment and 3 cycles after treatment, we collected 5 mL of fasting venous blood from the patients and centrifuged it to obtain the serum. The squamous cell carcinoma antigen (SCC) and cytokeratin 19 fragment (CYFRA21-1) were measured by the electrochemiluminescence method, and the carbohydrate antigen 50 (CA50) was detected via radioimmunoassay.

Health status and quality of life: We employed the KPS scale (range: 0-100 points) and the Function Assessment of Cancer Therapy-Lung (FACT-L; 0-100 points) to assess patients' health status and quality of life, respectively. The KPS score is inversely related to the patient's health status. FACT-L-based life quality assessments cover emotional, social, physical, and functional status, with the score being proportional to the life-quality level. Evaluations were conducted pre- and 3 cycles post-treatment.

Adverse events (AEs): AE severity grading followed the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Follow-up: Patient survival information was obtained from follow-up starting from the first treatment, with follow-up conducted through outpatient visits, phone calls, and other methods. Follow-up lasted for 2 years, once quarterly, recording PFS and OS.

Statistical methods

Statistical analysis utilized SPSS 26.0 (SPSS, IBM Corporation, Armonk, NY, USA). Categorical data (counts and percentages [%]) underwent chi-square testing. For measurement data, statistical presentation and analysis (between-groups) employed M (P25, P75) and the Kruskal-Wallis H test, respectively, if a non-normal distribution was followed; otherwise, the mean ± standard deviation and the t-test were used. Survival was visualized with the Kaplan-Meier method and compared by the Log-Rank test. Using univariate and multivariate Cox regression analyses, prognostic factors for OS and PFS were determined. In the univariate analysis, factors that had an impact on OS or PFS ($P<0.1$) were subsequently included in the multivariate analysis. This study uses two-sided hypothesis testing, with $P<0.05$ considered statistically significant.

Results

General data

This study enrolled 114 patients. Patient grouping was based on the treatment regime, with 41 of them being included in the ICIs group (24 males plus 17 females; mean age: 62) and 73 in the Endostatin+ICIs group (46 males and 27 females aged 61 years on average). There were 51 cases of adenocarcinoma and 54 patients with a ECOG stage ≤1 in the Endostatin+ICIs group, compared to the corresponding number of cases of 28 and 31 in the ICIs group. In this study, four ICIs were used,

Table 1. General data comparison

	ICIs (n=41)	Endostatin+ICIs (n=73)	χ^2/t	P
Gender			0.222	0.638
Male	24	46		
Female	17	27		
Age	62 (51, 66)	61 (55, 64)	0.041	0.968
Pathological type			0.030	0.862
Adenocarcinoma	28	51		
Squamous cell carcinoma	13	22		
Tumor staging			2.289	0.108
IIIb	16	18		
IV	25	55		
ECOG staging			0.037	0.847
0-1	31	54		
2	10	19		
Smoking history	18	40	1.246	0.264
Metastatic site				
Lung	15	30	0.224	0.636
Brain	6	9	0.122	0.727
Liver	4	6	0.236	0.627
Bone	13	23	0.000	0.982
Pleura	3	5	0.009	0.925
Immunosuppressive agent			0.222	0.934
Camrelizumab	16	31		
Sintilimab	12	20		
Pembrolizumab	7	13		
Tislelizumab	6	9		

namely camrelizumab, sintilimab, pembrolizumab, and tislelizumab. The two groups differed insignificantly in baseline characteristics (P<0.05). The median follow-up time was 11.3 monts, and the last follow-up time was on January 31, 2023, **Table 1**.

Treatment efficacy

In the Endostatin+ICIs group, 2 patients (2.74%) were found to have CR, while 14 (19.18%), 39 (53.42%), and 18 (24.66%) had PR, SD, and PD, respectively. Meanwhile, PR, SD, and PD were determined in 4 (9.76%), 15 (36.59%), and 22 (53.65%) in the ICIs group, respectively. The Endostatin+ICIs group showed a higher, though not reaching statistical significance, ORR than the ICIs group (21.92% vs. 9.76%; P=0.103), along with a statistically higher DCR (75.34% vs. 46.35%; P=0.002), as shown in **Table 2**.

Tumor marker levels

Baseline serum CYFRA21-1, SCC, and CA50 were similar across groups (P>0.05). Following three cycles of treatment, serum CYFRA21-1, SCC, and CA50 levels decreased in both cohorts (P< 0.05), especially in the Endostatin+ICIs group (P<0.05; **Table 3**).

Health status and quality of life

Pre-treatment KPS or FACT-L scores differed little across groups (P>0.05). After the three-cycle treatment, both scale scores elevated across groups, with even higher values in those receiving Endostatin+ICIs (P<0.05; **Tables 4** and **5**).

AEs

AEs, listed in **Table 6**, were comparable between groups (P>0.05). 26.03% of patients in the Endostatin+ICIs experienced grade 1-2 adverse events, while the corresponding proportion in the ICIs group was 34.14%. Grade 3-4 adverse events occurred in 3 cases in both the Endostatin+ICIs and ICIs groups (4.11% vs. 7.31%). Rh-Endo induced no notable increase in AEs, either in incidence or severity, nor was any clear cardiotoxicity identified. These AEs could all be managed through symptomatic treatment, and no deaths were caused by toxic and side effects.

Survival analysis

The mPFS showed a statistical inter-group significance (6.8 months with ICIs vs. 10.6 months with Endostatin+ICIs; P<0.001). The mOS in the Endostatin+ICIs group was 17.6 months, which was markedly longer than the 8.3 months in the ICIs group (P<0.001; **Figure 2**).

Table 2. Treatment response comparison

	CR	PR	SD	PD	Disease remission rate	Disease control rate
ICIs (n=41)	0 (0)	4 (9.76)	15 (36.59)	22 (53.65)	4 (9.76)	19 (46.35)
Endostatin+ICIs (n=73)	2 (2.74)	14 (19.18)	39 (53.42)	18 (24.66)	16 (21.92)	55 (75.34)
χ^2					2.684	9.695
P					0.103	0.002

Table 3. Comparative analysis of tumor markers

	CYFRA21-1 (ng/mL)		SCC (ng/L)		CA50 (U/mL)	
	Pre-treatment	Three cycles post-treatment	Pre-treatment	Three cycles post-treatment	Pre-treatment	Three cycles post-treatment
ICIs (n=41)	5.65±0.67	2.91±0.40	6.68±1.54	3.94±0.71	25.70±4.30	20.66±2.85
Endostatin+ICIs (n=73)	5.49±0.71	2.56±0.31	6.93±1.39	2.85±0.37	25.86±3.81	16.63±2.74
t	1.225	5.305	0.901	9.879	0.798	7.435
P	0.223	<0.001	0.370	<0.001	0.426	<0.001

Table 4. Comparative assessment of health status

	KPS	
	Pre-treatment	Three cycles post-treatment
ICIs (n=41)	67.54±3.67	74.20±4.51
Endostatin+ICIs (n=73)	68.40±3.79	77.85±3.45
t	1.176	4.849
P	0.242	<0.001

Analysis of independent prognostic factors for PFS

We performed univariate and multivariate Cox regression analyses to identify PFS-associated prognostic factors. In the univariate analysis, age and treatment approach emerged as factors influencing PFS and were therefore included in the multivariate analysis. Results demonstrated that both age (HR=1.037, P=0.012) and treatment approach (HR=0.368, P=0.004) were independent predictors (**Table 7**).

Analysis of independent prognostic factors for OS

OS-related determinants were further analyzed, also employing the univariate and multivariate Cox regression methods. In the univariate analysis, age, tumor stage and treatment approach emerged as factors influencing OS (P<0.1) for further multivariate analysis. Results demonstrated that treatment approach (HR=0.393, P=0.001) was an independent predictor (**Table 8**).

Discussion

Currently, there is no clear consensus on the pathogenesis of NSCLC. The occurrence of NSCLC has been shown to relate closely to various factors such as genetics, smoking, drinking, and the environment. These factors may exert varying degrees of influence on lung cell growth, proliferation, and genetic mutations, ultimately leading to the formation of cancer [28-30]. Due to the often inconspicuous early-stage symptoms, NSCLC diagnosis is quite challenging. Many patients are diagnosed at advanced stages, which leads to missing the best opportunity for surgical treatment. Research abroad has shown a 15% 5-year survival rate for advanced NSCLC and a median PFS of 8 months [31]. Chemotherapy remains the current first choice for most advanced NSCLC patients. The usual first-line treatment regimen involves platinum-based drugs combined with anti-angiogenic drugs or other chemotherapy drugs. Nowadays, ICIs have completely transformed NSCLC treatment [32]. The efficacy of PD-1/PD-L1 inhibitors as a single modality approach or in combination with chemotherapy in treating patients with advanced or metastatic NSCLC has been studied in many large-scale randomized III-phase trials. In the first-line setting, markedly extended median OS and median PFS are observed compared to sole chemotherapy [33].

Table 5. Comparative assessment of quality of life

	ICIs (n=41)		Endostatin+ICIs (n=73)	
	Pre-treatment	Three cycles post-treatment	Pre-treatment	Three cycles post-treatment
Physical well being	11.95±1.95	12.85±1.77*	11.14±2.26	14.27±2.06*,#
Social/family well being	11.05±2.00	16.29±1.75*	11.34±1.73	16.29±2.14*
Emotional well being	11.76±2.32	12.95±2.18*	11.11±2.16	13.51±2.35*
Functional well being	11.12±2.37	13.41±2.06*	10.85±2.66	14.42±2.08*,#
Lung caner subscale	10.44±1.61	15.24±3.10*	11.34±2.73	16.33±2.21*,#
Total	56.32±5.49	70.76±6.81*	55.78±6.05	74.82±7.31*,#

Notes: *P<0.05 vs. pre-treatment in the same group; #P<0.05 vs. ICIs group at the same time point.

Table 6. Incidence of adverse events

	ICIs (n=41)		Endostatin+ICIs (n=73)		χ^2	P
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4		
Total occurrences	14 (34.14)	3 (7.31)	19 (26.03)	3 (4.11)	1.496	0.221
Leukopenia	2	0	4	1	0.177	0.674
Anemia	3	1	6	1	0.169	0.681
Thrombocytopenia	2	0	2	0	0.355	0.552
Fatigue	2	0	5	0	0.208	0.649
Rash	4	2	6	1	0.661	0.416
Itching	2	0	3	0	0.037	0.848
Fever	1	0	2	0	0.009	0.923
Nausea and vomiting	2	0	2	0	0.355	0.552
Diarrhea	2	1	3	0	0.542	0.462
Hypertension	1	1	2	1	0.037	0.848
Albuminuria	1	0	1	0	0.174	0.677
Liver function impairment	1	0	1	0	0.174	0.677
Hypercreatininemia	0	0	1	0	0.567	0.452
Muscle soreness	1	0	1	0	0.174	0.677
Arthralgia	1	0	2	0	0.009	0.923
Hemoptysis	1	0	2	0	0.009	0.923
Adrenocortical insufficiency	0	0	1	0	0.567	0.452
Pneumonia	1	0	1	1	0.009	0.923
Myocarditis	0	0	1	0	0.567	0.452
Hypothyroidism	0	0	1	0	0.567	0.452

This study suggests that rh-Endo injection+ICIs can improve clinical efficacy and significantly prolong PFS and OS compared with ICIs alone. Rh-Endo injection, a 20 kD fragment of type VIII collagen, is an endogenous angiogenesis inhibitor, exerting a wide-ranging inhibitory activity on angiogenesis and growth in tumors [34]. Its anti-tumor effects have been confirmed in many clinical trials of solid tumors. For example, Chen et al. [35] showed that compared with placebo, rh-Endo injection-assisted chemotherapy improved the objective remission rate of breast cancer patients. Rh-Endo injection plus chemoradiotherapy contributes to significant PFS extension in head/neck squamous cell carcinoma and NSCLC. The tumor immune microenvironment has an important relationship with tumor neovascularization. Beyond suppressing the vascular network necessary for tumor expansion, anti-angiogenic inhibitors modulate the cancer microenvironment by facilitating immune effector cell proliferation and maturation, thereby enhancing immunotherapy effectiveness. Zhu et al. [12] pointed out that rh-Endo can exert anti-tumor effects. It achieves this by down-regulating VEGF expres-

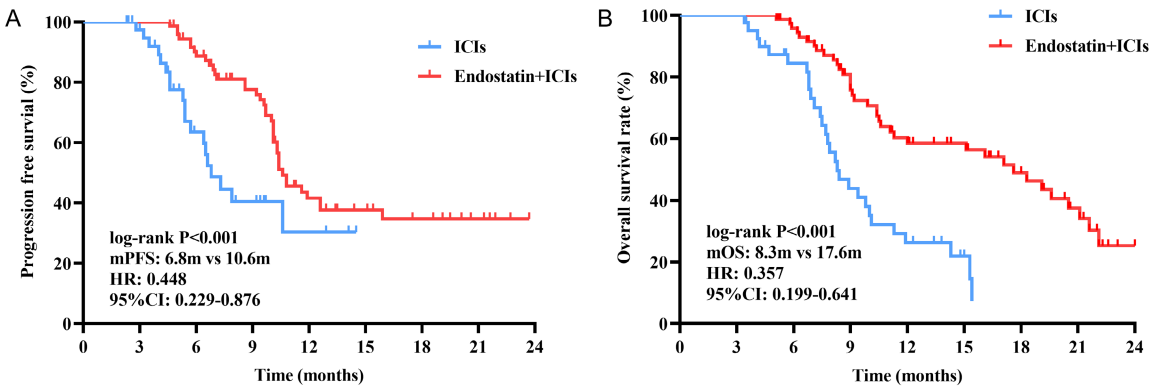

Figure 2. Survival analysis. A: Progression-free survival comparison; B: Overall survival comparison.

Table 7. Univariate and multivariate analyses of PFS

	Assignment	Univariate analysis			Multivariate analysis		
		HR	95% CI	P	HR	95% CI	P
Age	Continuous variable	1.031	1.002-1.061	0.038	1.037	1.008-1.068	0.012
Gender	0 = female, 1 = male	0.776	0.489-1.311	0.344	-	-	-
Pathological type	0 = squamous cell carcinoma, 1 = adenocarcinoma	0.793	0.457-1.376	0.410	-	-	-
Tumor Stage	0 = IIIb, 1 = IV	0.870	0.488-1.551	0.636	-	-	-
ECOG stage	0 = 0-1, 1 = 2	0.983	0.537-1.800	0.957	-	-	-
Smoking history	0 = no, 1 = yes	1.133	0.674-1.907	0.637	-	-	-
Treatment approach	0 = ICIs, 1 = Endostatin+ICIs	0.430	0.244-0.758	0.004	0.368	0.203-0.664	0.001

Table 8. Univariate and multivariate analyses of OS

	Assignment	Univariate analysis			Multivariate analysis		
		HR	95% CI	P	HR	95% CI	P
Age	Continuous variable	1.023	0.997-1.049	0.083	1.023	0.997-1.049	0.078
Gender	0 = female, 1 = male	0.988	0.596-1.639	0.964	-	-	-
Pathological type	0 = squamous cell carcinoma, 1 = adenocarcinoma	0.750	0.435-1.291	0.299	-	-	-
Tumor Stage	0 = IIIb, 1 = IV	0.587	0.336-1.023	0.060	0.621	0.355-1.086	0.095
ECOG stage	0 = 0-1, 1 = 2	0.906	0.506-1.624	0.740	-	-	-
Smoking history	0 = no, 1 = yes	1.046	0.638-1.715	0.859	-	-	-
Treatment approach	0 = ICIs, 1 = Endostatin+ICIs	0.386	0.221-0.675	0.001	0.393	0.224-0.687	0.001

sion, thereby reducing VEGFR activity, further decreasing the activity of vascular endothelial cells and inhibiting their proliferation. On the other hand, ICIs enhance antiangiogenic agents' efficacy via immune response restoration. Recombinant human endostatin, as an anti-angiogenic agent, possesses a specific mechanism of action targeting vascular endothelial growth factor (VEGF) [11]. It directly binds to VEGF and its receptors, blocking signal transduction pathways and thereby inhibiting VEGF's pro-angiogenic effects. Immune responses triggered by ICIs mount potent attacks against tumor cells. In response to this pressure, tumor cells correspondingly reduce VEGF production to avoid overstimulating the immune system. Furthermore, combination therapies may exert synergistic effects on the complex signaling networks within tumor cells. In addition, rh-Endo+ICIs can also effectively reduce tumor marker levels in patients' serum. Related studies have noted marked SCC and CA50 up-regulation in LC and other malignant tumors, correlating strongly with tumor invasion, occurrence, metastasis, and proliferation [36, 37]. CYFRA21-1, a type of cytokeratin, shows an evident rise in advanced NSCLC and is closely related to PFS, exhibiting predictive value for survival [40]. Rh-Endo may reduce the levels of these tumor markers by inhibiting the

growth and metastasis of tumor cells and thereby decreasing the tumor burden.

We also observed longer mPFS (10.6 months vs. 6.8 months) and mOS (17.6 months vs. 8.3 months) in Endostatin plus ICI-treated patients compared to ICI recipients. According to Yang et al. [38], among the patients recruited who received ICIs monotherapy and combination therapy, the combined use showed mPFS (8.3 months vs. 3.7 months; HR=0.276, 95% CI 0.125-0.607, P=0.001) and mOS benefits (18.0 months vs. 9.6 months; HR=0.364, 95% CI 0.147-0.902, P=0.009). Huang et al. [39] similarly showed that compared to sole ICIs, their combination with antiangiogenic drugs led to longer PFS and OS in advanced lung adenocarcinoma. However, in several existing studies evaluating single-agent ICIs as second-line or later-line treatments for advanced NSCLC, the ORR for both nivolumab and pembrolizumab monotherapy did not exceed 20%, with median progression-free survival (mPFS) falling short of 4 months [40, 41]. Although these studies cannot be directly compared, this study statistically demonstrated that the combination of recombinant human endostatin injection with ICIs is effective. Furthermore, we observed a comparable AE rate across groups. This shows that rh-Endo injection+ICIs not only has good synergistic anti-tumor effects, but also demonstrates no significant difference in safety compared to monotherapy. Previous studies have pointed out that compared with traditional endostatin, rh-Endo has a longer half-life, more amino acid sequences, and higher specificity, stability, and purity [42]. Finally, through Cox multivariate regression analysis, we identified treatment modality as a factor influencing patient PFS and OS. The combination of Endostatin+ICIs was identified as a protective factor, suggesting that Endostatin+ICIs may exert a synergistic effect in prolonging patient PFS.

This study also have several limitations. First, the limited sample size of this study may influence the results. Second, the treatment regimen involved four distinct ICIs, each with varying efficacy and safety profiles. Additionally, individual differences may introduce confounding effects on treatment outcomes. Meanwhile, as a retrospective investigation, the research design phase lacked systematic planning in variable selection, failing to identify essential variables based on the research questions. Constraints in data sources further hindered the full operationalization of variables. In multivariate Cox regression only included age, treatment method, and tumor stage. This seriously neglects other known, strong prognostic factors such as PD-L1 expression, TMB, and number of metastatic organs. Therefore, a large sample size, more comprehensive prospective study is needed to confirm the findings in this study.

To summarize, for NSCLC management, the rh-Endo injection-ICIs combination can provide PFS and OS benefits and greater quality-of-life improvement, without increasing treatment toxicity.

Disclosure of conflict of interest

None.

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