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Original Article

Alterations in peripheral blood inflammatory mediators, vascular endothelial growth factor, and serum tumor markers in advanced non-small cell lung cancer patients treated with bevacizumab combined with chemotherapy

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Abstract: Objectives: To investigate the effects of bevacizumab combined with chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). Methods: Clinical data of 120 patients with advanced NSCLC treated at Chongqing Hospital of Jiangsu Province Hospital between January 2023 and August 2025 were retrospectively analyzed. Patients were divided into two groups: the standard gemcitabine plus cisplatin chemotherapy group (SC group, n=60) and the bevacizumab combined with gemcitabine plus cisplatin group (SC+B group, n=60). Clinical efficacy was compared between the two groups after treatment. Results: After treatment, the objective response rate and disease control rate in the SC+B group were significantly higher than those of the SC group (P<0.05). The SC+B group also exhibited significantly higher levels of interleukin-1β, interleukin-2, interleukin-12, tumor necrosis factorα (TNF-α) and interferon-γ, along with decreased levels of vascular endothelial growth factor A and serum tumor markers (all P<0.05). Although serum immunoglobulin (Ig) G, IgM, IgA, as well as peripheral blood CD3+, CD4+, and CD4+/CD8+ ratio decreased in both groups after treatment, these indicators remained significantly higher in the SC+B group (all P<0.05). Serum creatinine and blood urea nitrogen levels increased in both groups, with no significant intergroup difference (all P>0.05). Scores of the Functional Assessment of Cancer Therapy-Lung and World Health Organization Quality of Life-BREF were significantly higher in the SC+B group (P<0.05). Furthermore, the incidence of hepatorenal dysfunction was lower in the SC+B group (P<0.05). Conclusions: Bevacizumab combined with chemotherapy can significantly improve clinical efficacy in patients with advanced NSCLC.

Keywords: Advanced non-small cell lung cancer, bevacizumab, inflammatory mediators, vascular endothelial growth factor, tumor markers

Introduction

Non-small cell lung cancer (NSCLC) is among the most prevalent and life-threatening malignant tumors worldwide, with its high prevalence posing a sustained threat to public health globally. The incidence of NSCLC is rising annually and imposes a heavy burden on global public health systems [1]. Data released by the World Health Organization indicate that lung cancer has long been the leading cause of cancer-related deaths worldwide, and NSCLC accounts for approximately 80%-85% of all newly diagnosed lung cancer cases [2]. The middle-aged and elderly population carries a significantly higher risk of lung cancer than other age groups. Since the early clinical manifestations of NSCLC are often vague and nonspecific, most patients are diagnosed at advanced stages (stage IIIb or IV) and thus miss the optimal opportunity for curative surgical resection [3]. Patients with advanced NSCLC tend to have a poor prognosis and short survival, and frequently suffer from severe symp-

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toms, including cough, dyspnea, and weight loss, accompanied by impaired quality of life. These conditions impose substantial psychological stress and economic burden on both patients and their families [4, 5]. Therefore, it is clinically imperative to maximize their quality of life and prolong survival within a reasonable therapeutic range.

Chemotherapy has long been the mainstay of treatment for advanced NSCLC. Combination regimens such as gemcitabine plus cisplatin can prolong survival and delay disease progression [6]. Effective multi-agent targeted therapeutic alternatives remain limited. For patients with advanced disease, the objective response and stable disease rate achieved by chemotherapy alone is seldom over 50%. Moreover, monochemotherapy yields limited improvement in the tumor microenvironment [7]. Compared to surgical resection, chemotherapy is associated with more systemic adverse health impacts. Treatment-related adverse events may impair patient treatment adherence; furthermore, compromised drug efficacy and poor treatment tolerance often necessitate dose reduction or treatment discontinuation, ultimately attenuating the antitumor efficacy of chemotherapeutic agents [8]. In recent years, anti-tumor therapies targeting tumor angiogenesis have developed rapidly. Bevacizumab, a humanized monoclonal antibody that specifically binds to vascular endothelial growth factor A (VEGF-A) to exert targeted antitumor activity, has attracted much attention for the treatment of advanced NSCLC [9, 10]. VEGF acts as a key regulator of tumor angiogenesis, tumorigenesis, and metastasis [11]. Bevacizumab specifically binds to VEGF-A and blocks its receptor binding, thereby inhibiting tumor angiogenesis, reducing tumor blood perfusion, and enhancing drug permeability in the tumor microenvironment [12]. Previous clinical studies have confirmed that combined treatment with bevacizumab plus conventional chemotherapy yields superior clinical benefits compared to chemotherapy alone: it improves objective tumor response rate, prolongs progression-free survival, and optimizes functional status and daily living ability in a considerable proportion of patients [13]. Based on the above clinical evidence, this study retrospectively analyzed clinical data from 120 patients with advanced NSCLC. We compared standard chemotherapy alone versus chemotherapy combined with bevacizumab in terms of therapeutic response, peripheral inflammatory mediators, VEGF-A levels and tumor marker expression. We also systematically evaluated patients' quality of life and the incidence of treatment-related adverse events. The present study aimed to explore the biological mechanisms and evaluate the clinical value of bevacizumab combined with chemotherapy, so as to provide evidence for individualized treatment strategies for advanced NSCLC.

Materials and methods

Baseline patient characteristics and enrolment data

Clinical data from 120 patients diagnosed with advanced NSCLC admitted and treated at Chongqing Hospital of Jiangsu Province Hospital between January 2023 and August 2025 were retrospectively analyzed. According to their actual treatment regimens, all enrolled patients were divided into two groups: the standard gemcitabine plus cisplatin chemotherapy group (SC) and the combined chemotherapy group (SC+B), with 60 patients in each group.

The sample size was determined as follows: A retrospective statistical power analysis showed that, for detecting a 20% difference in objective response rate (ORR) between groups, 60 cases per group achieved a statistical power of 85%, indicating adequate statistical efficiency. All consecutive patients who met the inclusion and exclusion criteria during the study period were enrolled to ensure data authenticity and completeness.

Inclusion criteria: ① Diagnosis consistent with the criteria for non-small cell lung cancer specified in the Chinese Society of Clinical Oncology Guidelines for the Diagnosis and Treatment of Primary Lung Cancer [14]; ② Clinical stage III or IV; ③ No prior thoracic surgery for lung cancer; ④ Expected survival time ≥3 months; ⑤ Karnofsky Performance Status score [15] >60; ⑥ No contraindications to chemotherapy.

Exclusion criteria: ① Severe combined multiple organ dysfunction; ② Concurrent other malignant tumors; ③ Accompanying immune dysfunction; ④ Positive lung cancer driver gene mutations; ⑤ Cognitive impairment or mental

disorders unable to cooperate with treatment; ⑥ Incomplete clinical data.

This study was approved by the Ethics Committee of Chongqing Hospital of Jiangsu Province Hospital.

Research methods

The SC group received gemcitabine plus cisplatin chemotherapy. The specific regimen was as follows: Gemcitabine Hydrochloride (Manufacturer: Lilly France S.A.S.; Approval Number: H20020180; Specification: 0.2 g/vial) 1.0 g/m^2 by intravenous infusion, administered once weekly. Cisplatin (Manufacturer: Jiangsu Hansoh Pharmaceutical Group Co., Ltd.; Approval Number: H20040813; Specification: 30 mg:6 mL) was given at a total dose of 80 mg/m^2 via intravenous infusion, divided into 3 doses. During chemotherapy, routine supportive and symptomatic treatments were administered, including gastroprotection, antiemetics, hepatoprotection, and adequate hydration. To prevent cisplatin-induced nephrotoxicity, furosemide (Manufacturer: Shanghai Hefeng Pharmaceutical Co., Ltd.; Approval Number: H31021063; Specification: 2 mL:20 mg) 20 mg was intravenously injected after cisplatin infusion, once daily for 3 consecutive days.

The SC+B group received bevacizumab (Manufacturer: Roche Pharma (Switzerland) Ltd.; Approval No.: S20120069; Specification: 400 mg/vial) in addition to the same gemcitabine plus cisplatin regimen. Bevacizumab was given at 7.5-15.0 mg/kg by intravenous infusion once every 3 weeks.

Patients in both groups were treated in 3-week cycles, with a total of 6 cycles completed.

Outcome measures

(1) Clinical efficacy evaluation: Efficacy was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [16]. Complete Response (CR): All measurable target lesions completely resolved, with no recurrence or new lesions for at least 4 consecutive weeks. Partial Response (PR): Residual tumor lesions remained; the sum of the largest cross-sectional diameters decreased by ≥50% from baseline, and this reduction was maintained for more than 4 weeks. Stable Disease (SD): No new malignant lesions appeared; the sum of lesion diameters decreased by <25% or increased by <25% relative to baseline. Progressive Disease (PD): New malignant lesions emerged, or the sum of lesion diameters increased by ≥25% from baseline, accompanied by continuous tumor growth and progression.

The ORR was defined as the proportion of patients achieving CR or PR. ORR (%) = (Case number of CR + Case number of PR)/Total case number × 100%. The disease control rate (DCR) included patients with CR, PR, and SD, calculated as the percentage of these patients in the total cohort. Both groups completed 6 treatment cycles.

(2) Detection of serum inflammatory and vascular endothelial growth factor (VEGF) levels: Before and after treatment, approximately 4 mL of fasting peripheral venous blood was collected from each patient. Blood samples were centrifuged to isolate serum, which was immediately stored at -80°C for subsequent detection. Serum levels of IL-1β, IL-2, IL-12, IFN-γ, TNF-α, and VEGF-A were measured using commercial ELISA kits strictly following the manufacturer's protocols. ELISA kits were purchased from Thermo Fisher Scientific, USA. All indices were quantified according to the standard curve. All experiments were independently performed twice in a blinded manner by two professional technicians to ensure accuracy and reproducibility.

(3) Detection of serum tumor markers: Before and after treatment, 4 mL of peripheral venous blood was collected from all patients. Samples were centrifuged to separate serum and stored immediately at -80°C until analysis. Serum levels of cytokeratin 19 fragments (CYFRA21-1), carcinoembryonic antigen (CEA), cancer-related antigen 125 (CA125), cancer-related antigen 19-9 (CA19-9), squamous cell carcinoma antigen (SCCA-g), and neuron-specific enolase (NE-SPAAg) were detected in strict accordance with the kit instructions. Related detection kits were supplied by Roche Diagnostics, Germany. All experimental procedures were strictly quality-controlled to ensure batch-to-batch consistency and reliable results.

(4) Disease-specific quality of life assessment: The quality of life of all enrolled patients was

evaluated at baseline and during treatment, in accordance with the standards specified in the Guidelines for Evaluating Quality of Life in Lung Cancer Patients, using the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale [17]. The scale consists of 36 items divided into four main domains: physical well-being, functional ability, emotional well-being, and social relationships, plus a lung cancer subscale (LCS). Each item is scored on a 0-4 scale, with a total possible score ranging from 0 to 144. Higher scores indicate better patient-reported quality of life. Interviews were conducted based on the scale, and the results will be used for monitoring changes in therapeutic effects throughout the study to control outcomes and track improvement.

(5) Measurement of immune function indicators: Fasting peripheral venous blood samples were collected from patients at baseline and after intervention. Serum was centrifuged, aliquoted, and stored at -80°C for subsequent detection. Serum concentrations of immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin A (IgA), as well as the percentages of CD3+ T lymphocytes, CD4+ T lymphocytes, and the CD4+/CD8+ ratio, were detected by immunoturbidimetry. All detection reagents were purchased from Roche, USA, and all procedures were performed strictly in accordance with routine operating standards. Two researchers independently repeated the measurements in different laboratories to verify accuracy and reliability.

(6) Monitoring of renal function values: Fasting peripheral venous blood samples were collected from subjects at baseline and during/after intervention. After collection, samples were centrifuged to separate serum, which was either immediately stored at -80°C or sent for testing. Serum creatinine (Scr) and blood urea nitrogen (BUN) levels were measured using a fully automated biochemical analyzer with matching kits. All test kits were purchased from Sysmex Corporation, Japan. Daily quality control was performed on laboratory instruments, and all indicator data were reviewed independently by two researchers to prevent operational human error and improve test accuracy.

(7) Universal quality of life assessment: The World Health Organization Quality of Life Brief version (WHOQOL-BREF) [18] was used to evaluate subjects' quality of life at both baseline and post-intervention. The scale includes 26 items covering four domains: physiology, psychology, social relationships, and environmental factors. Except for two independent items, all other items are scored on a 15 scale. After conversion using a standard formula, each domain score ranges from 0 to 100, with higher scores indicating better quality of life in that domain. The scale was administered by uniformly trained researchers who guided patients to complete it. For patients unable to complete it independently, researchers assisted to ensure data integrity and consistency. This scale was used to evaluate the impact of the intervention on patients' overall quality of life.

(8) Adverse reactions: During treatment, adverse reactions were recorded, including thrombocytopenia, leukopenia, myelosuppression, hepatorenal dysfunction, nausea, vomiting, and rash.

Statistical analysis

All statistical analyses were performed using SPSS 26.0 software (IBM Corp., Armonk, NY, USA). Normality tests were first performed on all quantitative data. Data conforming to a normal distribution were expressed as mean ± standard deviation (mean ± SD). Differences between the two groups were compared using independent-samples t-tests, while comparisons among multiple groups were performed using one-way analysis of variance (ANOVA), followed by LSD or Bonferroni correction for multiple pairwise comparisons. Data not conforming to a normal distribution were expressed as median (interquartile range) and compared between the two groups using the Mann-Whitney U test. Qualitative variables were expressed as case numbers and percentages (n/%), and intergroup comparisons were performed using the chi-square test or Fisher's exact test as appropriate. All statistical analyses were two-tailed, and a *P*-value <0.05 was considered significant.

Results

Comparison of baseline characteristics between the two groups

As shown in **Table 1**, there were no statistically significant differences between the SC group and the SC+B group in terms of age, sex, smoking history, pathological type, clinical stage, TNM stages, KPS score, and comor-

Table 1. Comparison of baseline clinical data between two groups of patients (example, n=60)

Baseline characteristic	SC group (n=60)	SC+B group (n=60)	$t/\chi^2/Z$	*P*
Age (years)	63.2±8.5	62.7±9.0	0.31	0.758
Gender			0.14	0.708
Man	38 (63.3)	40 (66.7)		
Female	22 (36.7)	20 (33.3)		
Smoking history			0.14	0.708
Have	35 (58.3)	37 (61.7)		
Nothing	25 (41.7)	23 (38.3)		
Pathological type			0.14	0.930
Squamous cell carcinoma	28 (46.7)	27 (45.0)		
Adenocarcinoma	32 (53.3)	33 (55.0)		
Clinical Staging			0.14	0.708
Phase III	25 (41.7)	27 (45.0)		
Phase IV	35 (58.3)	33 (55.0)		
TNM staging (T)			0.48	0.787
T2	12 (20.0)	14 (23.3)		
T3	28 (46.7)	27 (45.0)		
T4	20 (33.3)	19 (31.7)		
TNM staging (N)			0.45	0.799
N0	8 (13.3)	9 (15.0)		
N1	18 (30.0)	20 (33.3)		
N2	34 (56.7)	31 (51.7)		
TNM staging (M)			0.14	0.708
M0	25 (41.7)	27 (45.0)		
M1	35 (58.3)	33 (55.0)		
KPS rating	72.8±7.6	73.5±7.3	0.51	0.611
Comorbid disease			0.14	0.708
Hypertension	18 (30.0)	20 (33.3)		
Diabetes	10 (16.7)	9 (15.0)	0.07	0.794

Note: SC: standard chemotherapy; SC+B: standard chemotherapy + bevacizumab; KPS: Karnofsky Performance Status; CEA: carcinoembryonic antigen.

Table 2. Comparison of clinical efficacy (n/%)

Efficacy	SC group (n=60)	SC+B group (n=60)	χ^2 value	*P* value
CR	0/0.00	3/5.00		
PR	29/48.33	38/63.33		
SD	21/35.00	17/28.33		
PD	10/16.67	2/3.34		
ORR	29/48.33	41/68.33	4.35	0.019
DCR	50/83.33	58/96.66	5.04	0.011

Note: SC: standard chemotherapy; SC+B: standard chemotherapy + bevacizumab; CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ORR: Objective Response Rate; DCR: Disease Control Rate.

bidities (hypertension, diabetes mellitus) (all *P*>0.05). These results indicate that the baseline clinical characteristics of the two groups were well balanced and comparable before treatment.

Comparison of therapeutic response

As shown in **Table 2**, the post-treatment OR was 48.33% (29/60) in the SC group and 68.33% (41/6) in the SC+B group; the DCR was 83.33% (50/60) and 96.66% (58/60), respectively. Compared with the SC group, The SC+B group showed significantly higher ORR and DCR (both *P*<0.05).

Comparison of serum inflammatory mediators and VEG factor levels

After treatment, both the SC group and SC+B group exhibited significantly increased serum

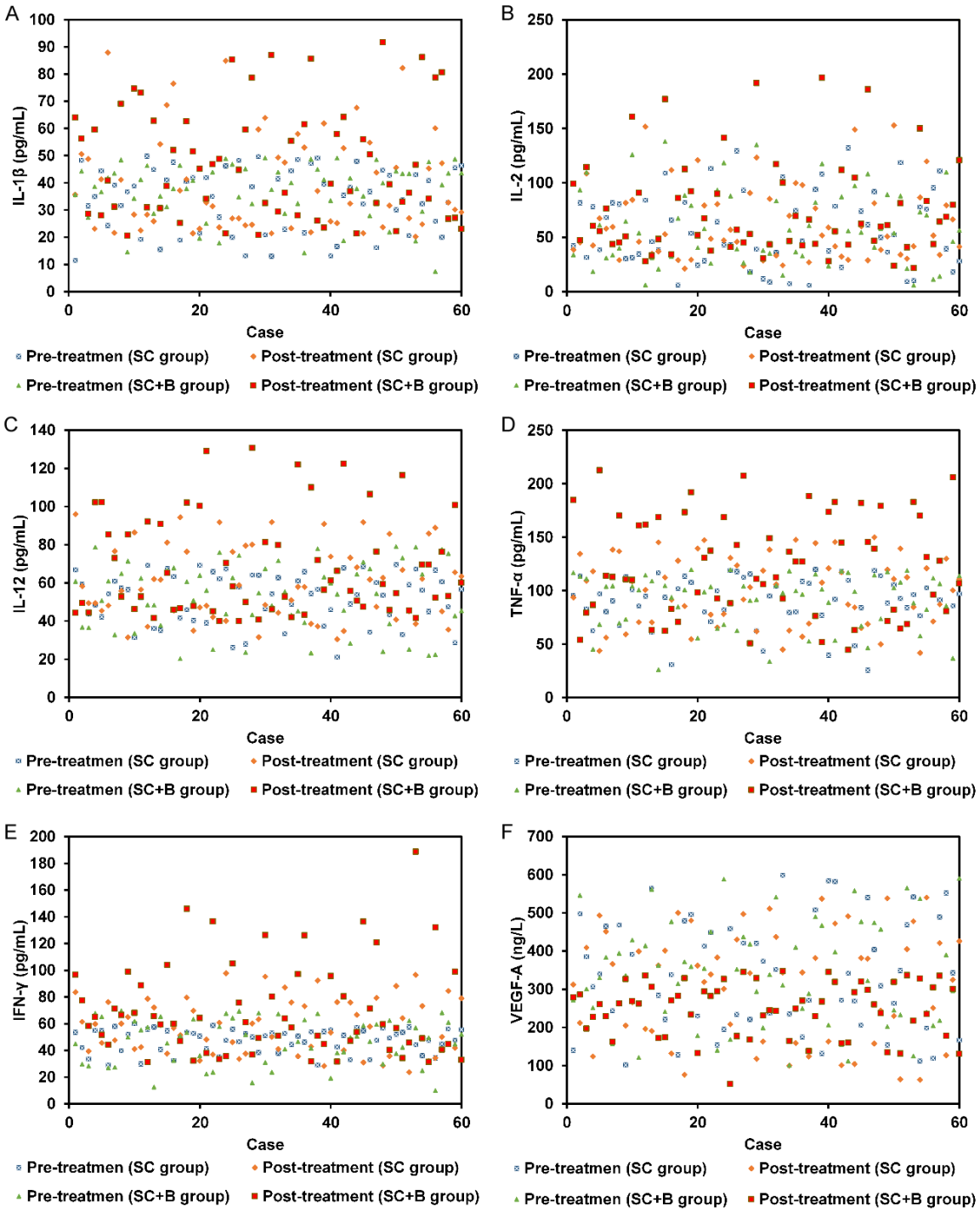

Figure 1. Comparison of serum inflammatory and vascular endothelial growth factor levels before and after treatment (SC group (n=60); SC+B group (n=60)). A. IL-1β: Interleukin-1β; B. IL-2: Interleukin-2; C. IL-12: Interleukin-12; D. TNF-α: Tumor necrosis factor-α; E. IFN-γ: Interferon-γ; F. VEGF-A: Vascular endothelial growth factor-A. Note: SC: standard chemotherapy; SC+B: standard chemotherapy + bevacizumab.

levels of IL-1β, IL-2, IL-12, TNF-α, and IFN-γ, and significantly decreased VEGF-A concentrations, compared with their respective pre-treatment levels (all $P<0.05$). Intergroup comparison showed that, compared to the SC group, the SC+B group had significantly higher post-treatment serum levels of IL-1β, IL-2, IL-12, and TNF-α, and significantly lower VEGF-A levels (with a reduction of more than 60%, all $P<0.05$) (**Figure 1**).

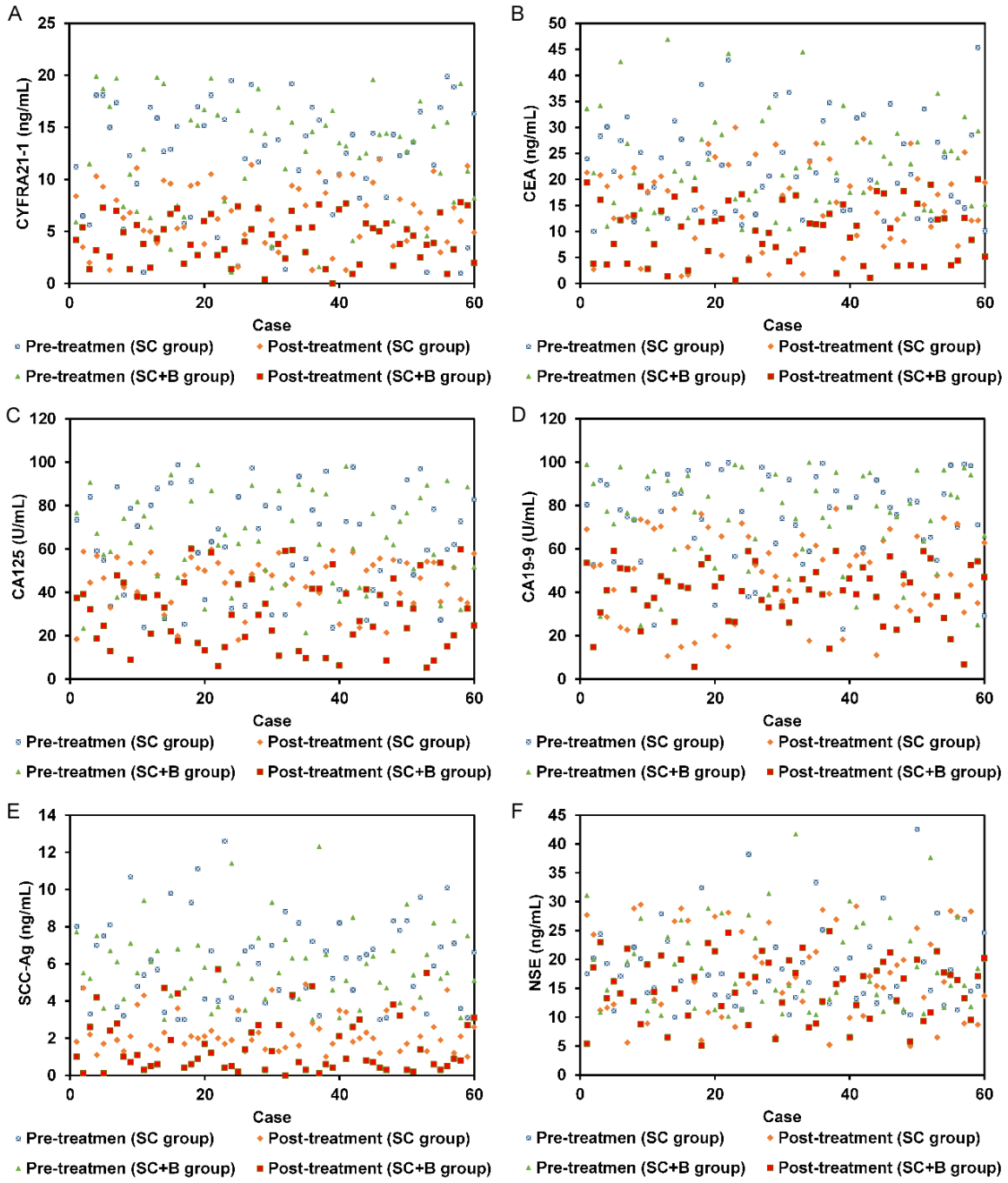

Figure 2. Comparison of serum tumour marker levels before and after treatment (SC group (n=60); SC+B group (n=60)). A. CYFRA21-1: Cytokeratin 19 fragment antigen; B. CEA: Carcinoembryonic antigen; C. CA125: Cancer antigen 125; D. CA19-9: Cancer antigen 19-9; E. SCC-Ag: Squamous cell carcinoma antigen; F. NSE: Neuron-specific enolase. Note: SC: standard chemotherapy; SC+B: standard chemotherapy+ bevacizumab.

Comparison of serum tumor marker concentrations

As illustrated in **Figure 2**, both groups showed significant reductions in serum CYFRA21-1, CEA, CA125, CA19-9, SCC-Ag, and NSE levels after treatment compared with pretreatment (all $P<0.05$). Furthermore, post-treatment serum concentrations of CYFRA21-1, CEA, CA125, CA19-9, SCC-Ag, and NSE in the SC+B group were significantly lower than those of the SC group (all $P<0.05$).

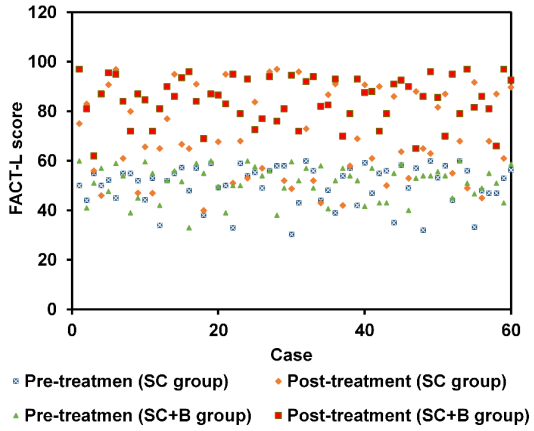

Figure 3. Comparison of quality of life functional assessment of cancer therapy - Lung (FACT-L) scores before and after treatment (SC group (n=60); SC+B group (n=60)). Note: SC: standard chemotherapy; SC+B: standard chemotherapy+ bevacizumab.

Comparison of FACT-L scores before and after treatment

As shown in **Figure 3**, after treatment, both the SC group and SC+B group had significantly higher FACT-L scores compared with their pretreatment levels ($P<0.05$). Additionally, the post-treatment FACT-L scores in the SC+B group were significantly higher than those of the SC group ($P<0.05$).

Comparison of immune function indicators before and after treatment

As shown in **Figure 4**, after treatment, serum IgG, IgM, and IgA levels, as well as CD3+%, CD4+%, and CD4+/CD8+ ratio, were significantly lower in both groups compared with their respective pretreatment levels (all $P<0.05$). After treatment, serum IgG, IgM, and IgA levels, as well as CD3+%, CD4+%, and CD4+/CD8+ ratio, were significantly higher in the SC+B group than in the SC group (all $P<0.05$).

Comparison of renal function indicators before and after treatment

As shown in **Figure 5**, after treatment, serum Scr and BUN levels were significantly higher in both groups compared to their respective pretreatment levels (both $P<0.05$). There was no significant difference in post-treatment serum Scr and BUN levels between the SC+B group and the SC group (both $P>0.05$).

Comparison of WHOQOL-BREF scores before and after treatment

As shown in **Figure 6**, after treatment, scores in the physiological, psychological, environmental, and social relationship domains of the WHOQOL-BREF were significantly higher in both groups compared to their respective pretreatment levels (all $P<0.05$). After treatment, scores in these four domains were significantly higher in the SC+B group than in the SC group (all $P<0.05$).

Comparison of adverse events

Table 3 shows the comparison of adverse events between the two groups. There were no significant differences in the incidence of adverse reactions such as nausea, vomiting, rash, thrombocytopenia, leukopenia, and myelosuppression between the SC group and the SC+B group (all $P>0.05$). The incidence of hepatorenal dysfunction was 38.33% (23/60) in the SC group, which was significantly higher than that of the SC+B group (20.00%, 12/60), and the difference was significant ($P<0.05$).

Discussion

NSCLC is the predominant histologic subtype of advanced lung cancer. Surgical options are limited for advanced patients, and chemotherapy has long been the primary treatment modality. Gemcitabine combined with cisplatin can improve patient survival but has limited efficacy, accompanied by significant myelosuppression and gastrointestinal adverse reactions [19]. As an anti-angiogenic targeted drug, bevacizumab inhibits tumor angiogenesis by blocking the VEGF-A signaling pathway [20, 21]. In recent clinical practice, the combination of bevacizumab and chemotherapy has demonstrated significant synergistic antitumor activity in advanced NSCLC [22]. Therefore, we conducted this study to explore the specific biological role and molecular mechanisms by which bevacizumab, combined with conventional chemotherapy, enhances clinical efficacy and alters serum biomarker profiles, through a comparative analysis of chemotherapy alone versus chemotherapy plus bevacizumab.

Elevated levels of inflammatory mediators may indicate enhanced innate and adaptive antitumor immunity in the host. IL-1β, an acute-phase

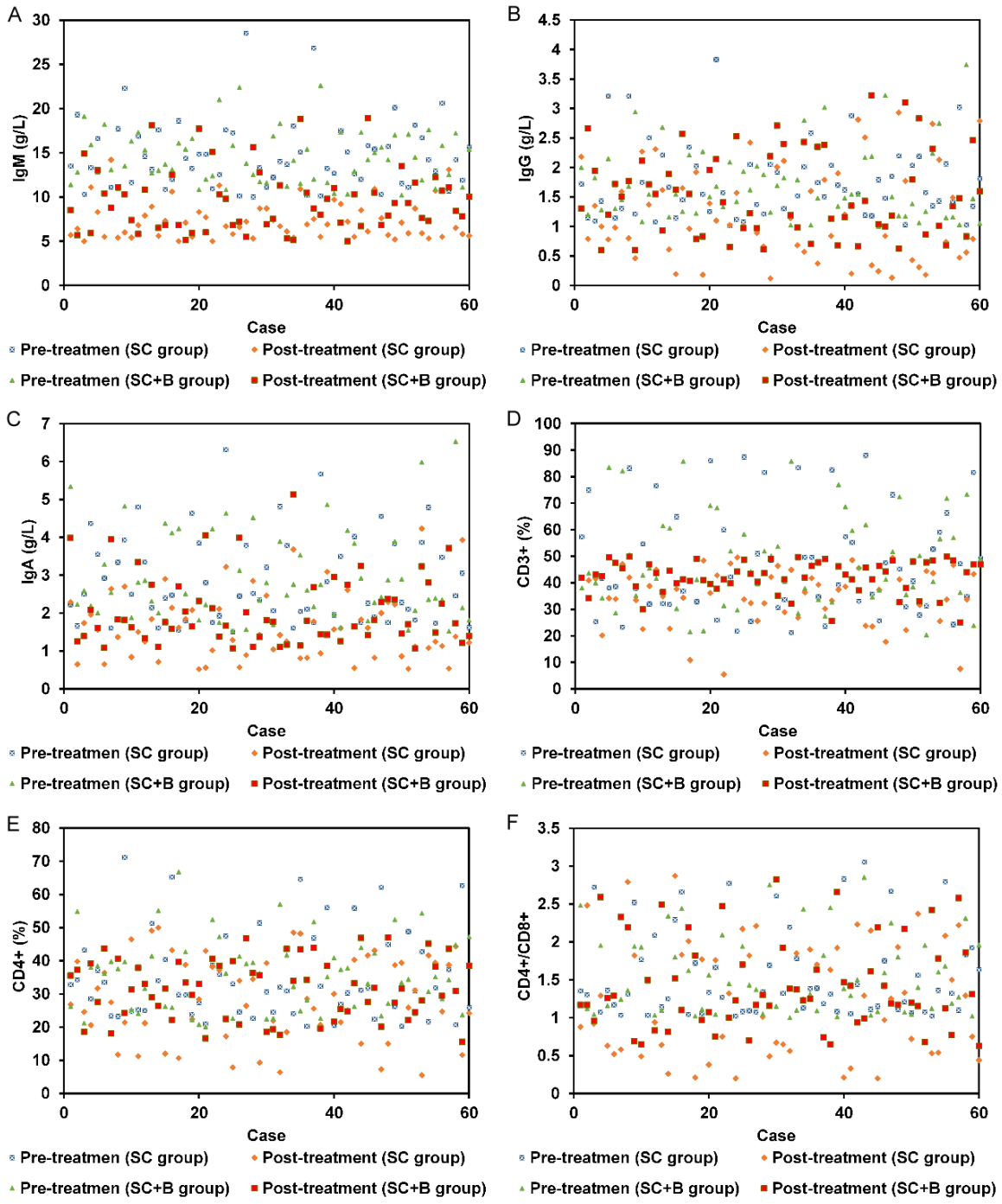

Figure 4. Comparison of immune function indicators before and after treatment (SC group (n=60); SC+B group (n=60)). A. IgG: Immunoglobulin G; B. IgM: Immunoglobulin M; C. IgA: Immunoglobulin A; D. CD3+: Percentage of CD3+ T lymphocytes; E. CD4+: Percentage of CD4+ T lymphocytes; F. CD4+/CD8+: CD4+/CD8+ ratio. Note: SC: standard chemotherapy; SC+B: standard chemotherapy + bevacizumab.

protein highly inducible by inflammatory stimuli, enhances tissue remodeling by altering the microenvironment or directly stimulating other cells [23]. IL-2 is a key factor regulating the clonal proliferation and functional maturation of T lymphocytes to enhance immune-mediated elimination of malignant cells [24]. IL-12 promotes the functional activity of T lymphocytes and natural killer cells, and induces downstream IFN-γ synthesis [25]. TNF-α drives

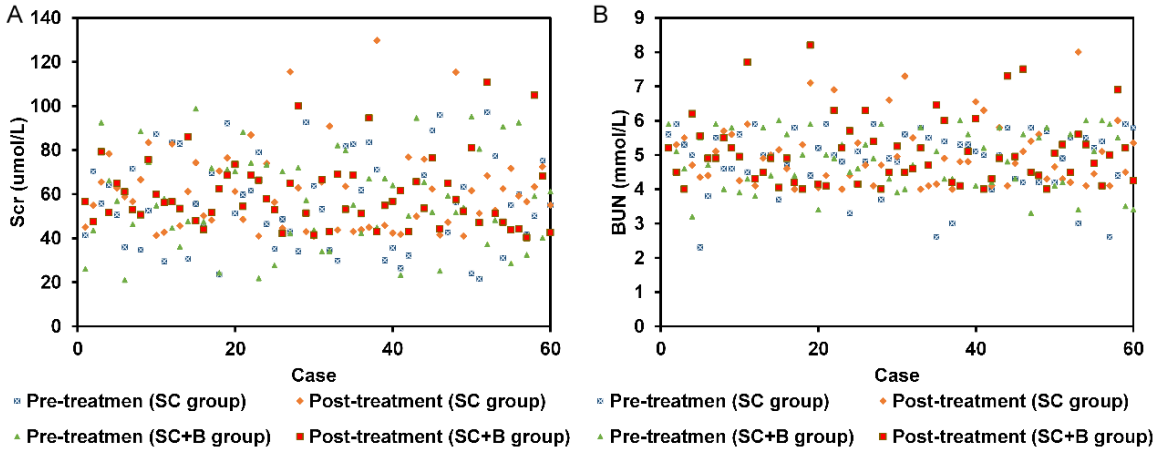

Figure 5. Comparison of renal function indicator levels before and after treatment (SC group (n=60); SC+B group (n=60)). A. Scr: Serum creatinine; B. BUN: Blood urea nitrogen. Note: SC: standard chemotherapy; SC+B: standard chemotherapy + bevacizumab.

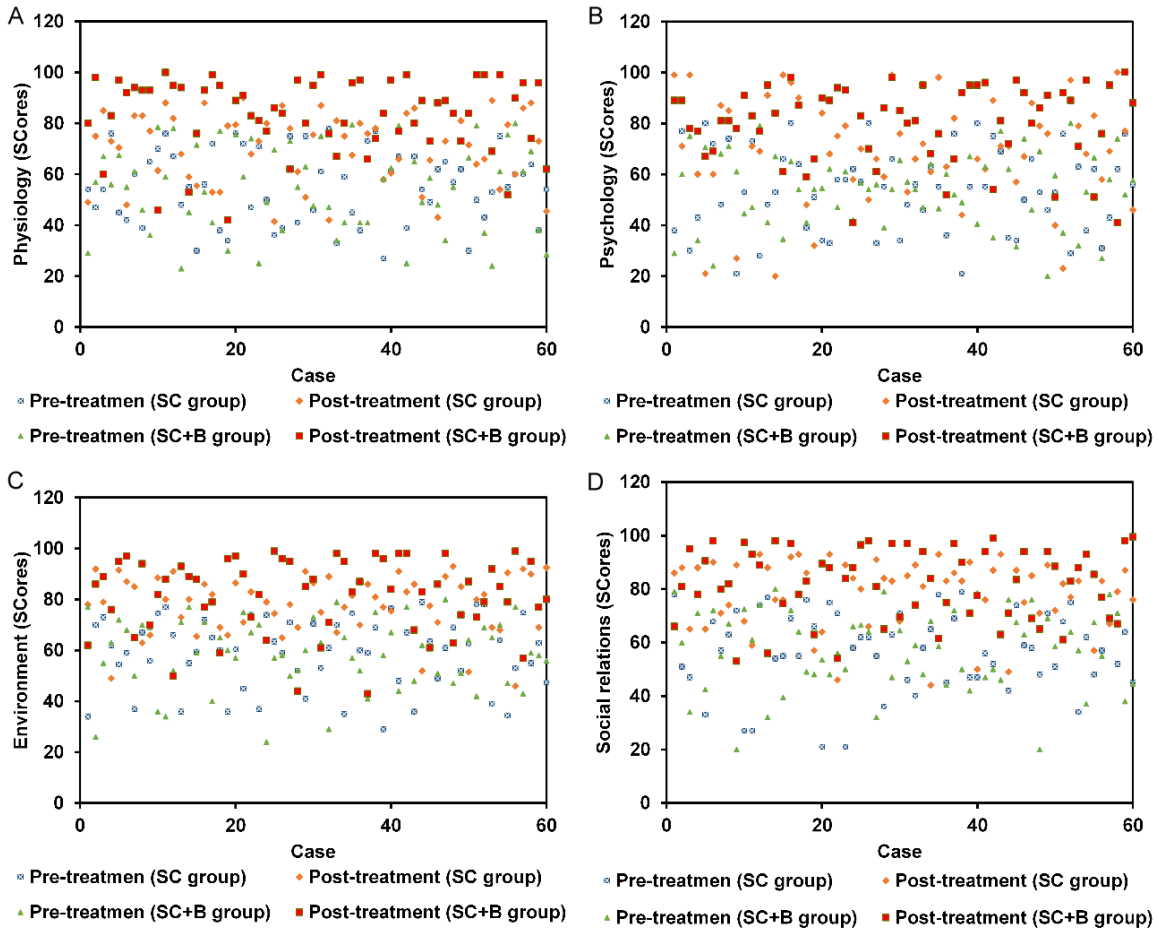

Figure 6. Comparison of World Health Organization quality of Life-BREF (WHOQOL-BREF) scores before and after treatment (SC group (n=60; SC+B group (n=60)). A. Physiological domain score; B. Psychological domain score; C. Environmental domain score; D. Social relationship domain score. Note: SC: standard chemotherapy; SC+B: standard chemotherapy + bevacizumab.

Table 3. Comparison of adverse reactions (n/%)

Adverse reaction	SC group (n=60)	SC+B group (n=60)	χ^2 value	*P* value
Nausea	30/50.00	29/48.33	0.03	0.85
Vomiting	29/48.33	25/41.67	0.54	0.464
Rash	26/43.33	25/41.67	0.03	0.854
Thrombocytopenia	21/35.00	13/21.67	2.58	0.108
Leukopenia	26/43.33	19/31.67	1.72	0.191
Bone Marrow Suppression	17/28.33	11/18.33	1.68	0.195
Liver & Kidney function impairment	23/38.33	12/20.00	4.73	0.032

Note: SC: standard chemotherapy; SC+B: standard chemotherapy + bevacizumab.

inflammatory processes, induces tumor cell necrosis, and enhances sensitivity to cytotoxic agents [26]. IFN-γ enhances immune surveillance by regulating the composition and function of the tumor-associated immunogenic microenvironment, thereby promoting T cell responses against cancerous tissues [27]. The results of this study showed that advanced NSCLC patients receiving adjuvant bevacizumab treatment had significantly higher plasma levels of several cytokines (IL-1β, IL-2, IL-12, TNF-α, and IFN-γ) compared to those of the SC group. Incorporating bevacizumab into treatment strategies significantly increases tumor-infiltrating immune factors (e.g., TNF-α, IFN-γ); *in vitro* and *ex vivo* models have shown that this reduces resistance to chemotherapeutic drugs. Additionally, the current study found that advanced NSCLC patients treated with combination therapy had significantly lower serum VEGF-A concentrations. Significant reduction in VEGF-A strongly supports that bevacizumab exerts potent anti-angiogenic activity by inhibiting tumor angiogenesis and reducing nutrient supply, thereby enhancing the sensitivity of tumor cells to chemotherapeutic drugs when co-administered [28].

Reduced tumor marker levels provide strong indirect evidence of tumor regression and response to chemotherapy. The results showed that advanced NSCLC patients treated with conventional chemotherapy combined with bevacizumab had significantly lower concentrations of CYFRA21-1, CEA, CA125, CA19-9, SCC-Ag, and NSE compared to those treated with chemotherapy alone. CYFRA21-1, a cytokeratin 19 fragment antigen, is a specific marker for NSCLC (especially squamous cell carcinoma), reflecting tumor burden and cell destruction [29]. CEA, a carcinoembryonic antigen, can be used to evaluate the efficacy of various solid tumors [30]. CA125 and CA19-9 can reflect tumor burden [31]. SCC-Ag is a squamous cell carcinoma-specific antigen used to monitor the efficacy of squamous cell carcinoma [32]. NSE, a neuron-specific enolase, is commonly used to monitor small cell lung cancer and a subset of NSCLC cases [33]. The decreasing trend in these tumor biomarkers indicates reduced tumor burden and enhanced susceptibility to chemotherapy [34]. The biological mechanism may be related to bevacizumab-mediated suppression of the VEGF-A signaling pathway, remodeling of the tumor microenvironment, and increased penetration of chemotherapeutic agents into tumor tissue, thereby enhancing the cytotoxic effect on malignant cells.

The results of this study showed that the bevacizumab combined with chemotherapy regimen had significant advantages in improving immune function, protecting organ function, and enhancing quality of life in advanced NSCLC patients. At the immune function level, although immunoglobulin (IgG, IgM, IgA) levels decreased in both groups after treatment compared with pretreatment - possibly related to the non-specific inhibitory effect of chemotherapy on the humoral immune system - the decrease was significantly smaller in the SC+B group than in the SC group. This suggests that the addition of bevacizumab may have partially attenuated the impact of chemotherapy on humoral immunity. For T lymphocyte subpopulation indicators reflecting cell-mediated immunity (CD3+%, CD4+%, and CD4+/CD8 ratio), both treatment groups showed decreases after treatment, but the decrease was significantly smaller in the combination therapy group than in the monotherapy group. Based on this, it is suggested that bevacizumab does not

directly enhance or suppress the host immune system; instead, by inhibiting angiogenesis (reducing tumor vessel density) or through other mechanisms (such as increasing tumor oxygen tension), vascular normalization may promote the infiltration of immune cells and improve antitumor immunity. In terms of renal safety, the data showed that Scr and BUN levels increased in both groups after treatment, indicating a certain degree of nephrotoxicity associated with chemotherapeutic drugs such as cisplatin. However, there was no significant difference in post-treatment Scr and BUN levels between the two groups, suggesting that adding bevacizumab does not increase renal burden under routine hydration and monitoring, confirming the renal safety of this combination regimen. Improvements in quality of life were further confirmed by the WHOQOL-BREF evaluation: the SC+B group had significantly higher scores in the physiological, psychological, environmental, and social relationship domains compared with the SC group. These benefits were not only due to the superior tumor control of combination therapy, which alleviated disease symptoms, but also possibly related to the lower incidence of hematopoietic dysfunction and hepatorenal damage compared to monotherapy, leading to better overall physical condition after chemotherapy (enhanced physical vitality and positive mood).

In addition, the data from this study showed that advanced NSCLC patients treated with conventional chemotherapy combined with bevacizumab had significantly higher ORR and DCR compared to those treated with chemotherapy alone. The combination therapy also increased FACT-L scores and reduced the incidence of hepatorenal damage. This study observed an improved response rate with bevacizumab, as well as a longer disease-free interval and better quality of life. This phenomenon may be due to the selective targeting of tumor-associated blood vessels by bevacizumab, without promoting proliferation in normal tissues [35]. Meanwhile, combination therapy allows for reasonable dose reduction of chemotherapeutic drugs that cause excessive damage to normal tissues, thereby enhancing patient tolerance during treatment [36].

The originality of this study lies in the first systematic simultaneous evaluation of the comprehensive regulatory effects of bevacizumab combined with chemotherapy on peripheral blood inflammatory cytokines (IL-1β, IL-2, IL-12, etc.), angiogenesis marker (VEGF-A), and broad-spectrum tumor markers (including NSE, CYFRA21-1, etc.) in advanced NSCLC patients. Unlike previous studies that focused only on single indicators or survival rates, the data from this study revealed that this regimen exerts synergistic effects through multiple mechanisms, including anti-angiogenesis, immune regulation, and tumor burden reduction. The clinical significance of this study is mainly reflected in two aspects: (1) The results showed that the SC+B group had a significantly higher ORR (68.33%) than the SC group, with a lower incidence of adverse reactions (e.g., myelosuppression, hepatorenal dysfunction). This provides strong real-world evidence for clinicians for formulating first-line treatment strategies for advanced NSCLC, supporting the priority of bevacizumab combined with chemotherapy to balance efficacy and safety. (2) The study found that significant reductions in serum VEGF-A and specific inflammatory cytokines (e.g., IL-12, IFN-γ) were closely associated with decreased tumor markers, suggesting that these serological indicators could serve as non-invasive biomarkers for early prediction of treatment efficacy in future clinical practice, facilitating dynamic adjustment and individualized management of treatment regimens.

However, this study has several limitations. First, it is a single-institution retrospective analysis, which is prone to selection bias. Second, the sample size was limited, and further verification is needed through multi-institutional prospective studies. Third, long-term follow-up data, mortality rate, and disease-free survival data were lacking; fourth, the detailed mechanisms were not evaluated by examining immune cells in the tumor microenvironment after combination therapy. Therefore, future studies can further extend follow-up results and include molecular typing to explore the response of different patients to this combination therapy. Collectively, the findings of this study provide strong and reliable evidence for the implementation of individualized treatment strategies for advanced NSCLC, and further suggest that bevacizumab combined with chemotherapy has significant value in improving therapeutic response, regulating serum inflam-

matory markers and VEGF-A expression, reducing tumor marker levels, and optimizing overall physical function.

Conclusion

Bevacizumab combined with chemotherapy significantly improved the ORR and DCR in advanced NSCLC patients, positively regulated serum inflammatory cytokine and VEGF-A levels, reduced circulating tumor marker levels, improved quality of life, and lowered the incidence of adverse events such as hepatorenal dysfunction. These findings confirm that this combined therapeutic regimen has distinct clinical advantages and satisfactory safety in the treatment of advanced NSCLC.

Disclosure of conflict of interest

None.

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