

## Original Article

# Efficacy of DC-CIK-based immunotherapy combined with chemotherapy in the treatment of intermediate to advanced non-small cell lung cancer

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**Abstract:** Objective: To evaluate the efficacy of dendritic cell-cytokine-induced killer cell (DC-CIK)-based immunotherapy combined with chemotherapy in the treatment of intermediate to advanced non-small cell lung cancer (NSCLC) and its effect on the levels of serum carbohydrate antigen 199 (CA199), matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1). Methods: Sixty patients with intermediate to advanced NSCLC who were treated in the Department of Oncology of Jiangxi Cancer Hospital from January to June 2016 were grouped according to a randomized double-blind method, including the control group (CG, n=30) receiving a routine chemotherapy regimen and the experimental group (EG, n=30) receiving DC-CIK immunotherapy plus a routine chemotherapy regimen. The treatment efficacy, major adverse reactions, immune function, level of cytokines in peripheral blood, serum tumor markers and CA-199, MMP-9, TIMP-1 and vascular endothelial growth factor (VEGF) levels were compared between the two groups. Results: The overall cancer control rate of treatment in the EG (70.00%) was slightly higher than that in the CG (56.67%) ( $P > 0.05$ ). The peripheral blood CD4<sup>+</sup> and natural killer (NK) cell levels in the EG after treatment were higher than those in the CG, while interleukin-4 (IL-4), interferon- $\gamma$  (IFN- $\gamma$ ), transforming growth factor- $\beta$  (TGF- $\beta$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), CA199, carbohydrate antigen 125 (CA125), CYFRA211, carcinoembryonic antigen (CEA), MMP-9, TIMP-1, and VEGF levels in the EG were lower than those in the CG ( $P < 0.05$ ). Conclusion: DC-CIK immunotherapy combined with routine chemotherapy in the treatment of intermediate to advanced NSCLC had significant efficacy in enhancing patients' cellular immune function, reducing the inflammatory response, regulating tumor marker levels, and inhibiting tumor invasion and metastasis, without increasing adverse reactions.

**Keywords:** Intermediate to advanced non-small cell lung cancer, DC-CIK immunotherapy, CA199, MMP-9, TIMP-1

## Introduction

Lung cancer is the most common cancer in men and the third most common cancer in women. There were 2 million new cases in 2018, and non-small cell lung cancer (NSCLC) accounts for 80%-85% of all lung cancer, with a 5-year survival rate of about 15% [1, 2]. Due to the subtle symptoms and lack of specificity, most patients are already in an inoperable, intermediate to advanced stage at the time of diagnosis and usually receive platinum-based chemotherapy regimens [3]. However, as NSCLC mostly occurs in middle-aged and elderly patients, they often show poor drug tolerance

[4, 5] due to diminished drug clearance and reduced bone marrow reserve and immune function. As a result, researchers have been exploring a combination therapy that could suppress the tumor growth, improve immune function and control the rate of aberrant growth.

With the integration of immunology and molecular biology, bioimmunotherapy has been highly valued clinically for its advantages such as high efficiency and low toxicity, and this technology activates the body's immune system's ability to recognize tumors, thus achieving the purpose of inhibiting tumor growth, metastasis and recurrence [6, 7]. Dendritic cell-cytokine-

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induced killer cell (DC-CIK) immunotherapy refers to an immunotherapy regimen that co-cultures DC cells and CIK cells, with the former being antigen-presenting cells that can inhibit immune escape and have HLA compatibility, and the latter being antitumor and antiviral effector cells with strong tumoricidal activity, rapid proliferation, and high anti-apoptotic properties, and the cell population produced by co-culture of the two has stronger proliferative activity and anti-tumor ability [8-10]. The results of a meta-analysis have confirmed that DC-CIK immunotherapy combined with chemotherapy can enhance the near- to mid-term survival rate and improve the quality of life in patients with malignancy [11]. To further confirm the efficacy of DC-CIK immunotherapy, this study evaluated the efficacy of DC-CIK immunotherapy combined with chemotherapy in the treatment of intermediate to advanced NSCLC and the effects on serum carbohydrate antigen 199 (CA199), matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) levels.

### Materials and methods

#### Baseline data

Sixty patients with intermediate to advanced NSCLC who were treated in the Department of Oncology of Jiangxi Cancer Hospital from January to June 2016 were enrolled and divided into two groups (n=30 for each group) according to a randomized double-blind method. Inclusion criteria: patients met the diagnostic criteria of NSCLC [12] and tissue was confirmed by cytology and pathology, stage IIIA-IV; Karnofsky score  $\geq 60$ , expected survival time  $\geq 6$  months; patients with measurable lesions; no contraindications to chemotherapy or DC-CIK; no abnormalities in the electrocardiogram (ECG) or blood count; patients voluntarily signed the informed consent. Exclusion criteria: patients with extensive metastases in the central nervous system as well as in the liver, kidneys, supraclavicular lymph nodes, etc.; patients with organ failure, other types of malignancies; patients with long-term use of immunological agents; patients with mental, consciousness and speech disorders; patients with malignant pleural and abdominal effusions; patients with coagulation disorders; patients with history of major surgery and trau-

ma within one month of study enrollment; patients with an allergy to biological immunological agents. This study was approved by the Ethics Committee of Jiangxi Cancer Hospital.

#### Methods

(1) Basic treatment. Nutritional support, antiemetic, and symptomatic treatment were provided.

(2) Control group (CG) received a routine chemotherapy regimen. Squamous carcinoma was treated with gemcitabine + cisplatin. On the 1st and 8th days of treatment, an intravenous infusion of 1.0 g/m<sup>2</sup> gemcitabine was given (Specification: 200 mg, Jiangsu Hansoh Pharmaceutical Group Co. Ltd., H20030104) + 100 mL 0.9% sodium chloride injection. On the 1st-4th days of treatment, an intravenous infusion of 75 mg/m<sup>2</sup> cisplatin was given (Specification: 20 mg/dose, Jiangsu Hansoh Pharmaceutical Group Co. Ltd., H20040813) + 500 mL 0.9% sodium chloride injection. Adenocarcinoma was treated with pemetrexed + cisplatin chemotherapy. On the 1st day of treatment, intravenous infusion of 500 mg/m<sup>2</sup> pemetrexed (Specification: 200 mg/dose, Jiangsu Hansoh Pharmaceutical Group Co. Ltd., H20051288) + 100 mL 0.9% sodium chloride injection; 1st-4th days of treatment, intravenous infusion of 75 mg/m<sup>2</sup> cisplatin (Specification: 20 mg/dose, Jiangsu Hansoh Pharmaceutical Group Co. Ltd., H20040813) + 500 mL 0.9% sodium chloride injection was provided. The treatment continued for 2 cycles in total, with one month as one treatment cycle.

(3) Experimental group (EG) received a routine chemotherapy regimen (the same as CG) + DC-CIK immunotherapy. One day before chemotherapy, 100 mL of fasting peripheral blood was collected and centrifuged for 10 min (2000 r/min, r=8 cm). Lymphocyte isolates were centrifuged for 20 min. The white membrane layer was aspirated, and the peripheral blood mononuclear cell was obtained, centrifuged for 8 min, washed twice, and the counts were calculated. Cell concentration was adjusted to  $2 \times 10^6$  cells/mL and inoculated into 6-well plates for 2 h. The supernatant medium was discarded and the cells were incubated using interleukin-4 (IL-4) and DC complete medium. On the 5th day, incubation was continued after addition of tumor-specific antigen. On the 6th day, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )

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was used to induce the maturation of DC cells. On the 7-8th days, DC cells were harvested. After obtaining mononuclear cells, 1000 U/mL of recombinant human interferon for injection (size: 1 mL: 1 million IU, 1 mL: 3 million IU,) was added, and the cell concentration was adjusted to  $2 \times 10^6$  cells/mL, followed by incubation. On the 2nd day of treatment, 50 ng/mL CD3 monoclonal antibody and 1000 U/mL recombinant human interleukin-2 (IL-2) were added, and IL-2 and medium were supplemented depending on cell growth rate for 10-14 days. Chemotherapy was avoided during infusion. A course of DC-CIK treatment included 3 applications of DC and 5 applications of CIK infusion, and each patient completed at least 2 courses. The infusion was performed between DC and CIK twice daily for consecutive 4 days.

### Outcome measurement

(1) Curative effect. After 2 cycles of treatment, the treatment efficacy was evaluated with reference to the Evaluation Criteria for the Efficacy of Solid Tumors (RECIST) [13]: Total disappearance of lesions without new lesions for > 4 weeks was considered complete remission (CR); reduction of the sum of the longest diameter of lesions by > 30% for > 4 weeks was considered partial remission (PR); reduction of the sum of the longest diameter of lesions by < 30% or increase of < 20% was considered stable disease (SD); and the presence of new lesions or increase of the sum of the longest diameter of lesions by > 20% was considered disease progression (DP). Overall remission rate (ORR) = CR rate + PR rate and disease control rate (DCR) = CR rate + PR rate + SD.

(2) Laboratory indicators. Three mL of fasting peripheral blood was collected one day before and 2 cycles after treatment, centrifuged, and the supernatant was refrigerated at  $-20^{\circ}\text{C}$ .  $\text{CD4}^+$  and natural killer (NK) cells were determined using a MACSQuant<sup>®</sup> Analyzer 16 high-throughput flow cytometer (Metenyi Biotech GmbH, Germany). The levels of interferon- $\gamma$  (IFN- $\gamma$ ), transforming growth factor- $\beta$  (TGF- $\beta$ ), TNF- $\alpha$ , CA199, carbohydrate antigen 125 (CA125), CYFRA211, carcinoembryonic antigen (CEA), MMP-9, TIMP-1, and vascular endothelial growth factor (VEGF) were determined using enzyme-linked immunosorbent assay (ELISA) kits (Shenzhen Xinbosheng Biotechnology Co.).

(3) Adverse reactions. The incidence of adverse reactions, including leukopenia, thrombocytopenia, gastrointestinal reactions, and bone marrow suppression, were determined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [14]. If the neutrophil granulocyte was less than  $2.0 \times 10^9/\text{L}$ , it was considered neutropenia; if the platelet count was lower than  $70 \times 10^9/\text{L}$ , it was considered thrombocytopenia.

### Statistical analysis

With SPSS 24.0, measurement data were expressed as  $\bar{x} \pm s$ , independent sample t and paired sample t test were used for comparison between groups and within groups. Count data were expressed as [n (%)] and were examined using  $\chi^2$  test. Graphpad prism 8.0 was used as the graphic software.  $P < 0.05$  indicated that the difference was statistically significant.

## Results

### Baseline data

The CG included 19 males and 11 females, aged ( $58.7 \pm 3.2$ ) years, with 15 cases of adenocarcinoma and 15 cases of squamous carcinoma, whereas the EG included 18 males and 12 females, aged ( $59.1 \pm 3.6$ ) years, with 16 cases of adenocarcinoma and 14 cases of squamous carcinoma. The general information of the EG was not significantly different from the CG ( $P > 0.05$ ) (Table 1).

### Therapeutic efficacy

The ORR of the EG (26.67%) was not significantly different from that of the CG (16.67%) ( $P > 0.05$ ). The DCR of treatment in the EG (70.00%) was slightly higher than that in the CG (56.67%) ( $P > 0.05$ ), indicating that DC-CIK immunotherapy combined with chemotherapy was effective in the treatment of intermediate to advanced NSCLC and could inhibit the progression of the disease (Table 2).

### Immune function

In order to observe the effect of DC-CIK immunotherapy combined with chemotherapy on the immune function of patients, the changes of  $\text{CD4}^+$  and NK cell levels in the peripheral blood of patients in the two groups were detected by

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**Table 1.** Comparison of baseline data between two groups (n/χ±S)

Group	Male/female	Age (years)	Tumor type	TNM Staging
			Adenocarcinoma/Squamous carcinoma	Stage IIIA/Stage IIIB/Stage IV
Control group (n=30)	19/11	58.7±3.2	15/15	2/5/23
Experimental group (n=30)	18/12	59.1±3.6	16/14	3/6/21
X <sup>2</sup> /t	0.071	0.455	0.067	0.019
P	0.791	0.651	0.792	1.000

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

Group	CR	PR	SD	DP	Total remission rate	Total control rate
Control group (n=30)	0 (0.00)	5 (16.67)	12 (40.00)	13 (43.33)	5 (16.67)	17 (56.67)
Experimental group (n=30)	0 (0.00)	8 (26.67)	13 (43.33)	9 (30.00)	8 (26.67)	21 (70.00)
X <sup>2</sup>					0.884	1.148
P					0.347	0.284

flow cytometry. The results showed that there was no significant difference in the levels of CD4<sup>+</sup> and NK cells in the peripheral blood between the two groups before treatment ( $P > 0.05$ ). After treatment, the levels of CD4<sup>+</sup> and NK cells in the peripheral blood of both groups were higher than those before treatment ( $P < 0.05$ ). The CD4<sup>+</sup> and NK cell levels were higher in the EG after treatment than those in the CG ( $P < 0.05$ ), indicating that DC-CIK immunotherapy combined with chemotherapy improved the cellular immune function of patients (**Figure 1**).

### Peripheral blood cytokines

In order to observe the effect of DC-CIK immunotherapy combined with chemotherapy on peripheral blood cytokines, the levels of IL-4, IFN- $\gamma$ , TGF- $\beta$  and TNF- $\alpha$  in the peripheral blood of patients in the two groups were detected by ELISA. The results showed that there was no significant difference in the levels of IL-4, IFN- $\gamma$ , TGF- $\beta$  and TNF- $\alpha$  in the peripheral blood between the two groups before treatment ( $P > 0.05$ ). After treatment, the levels of IL-4, IFN- $\gamma$ , TGF- $\beta$  and TNF- $\alpha$  in the peripheral blood of both groups were lower than those before treatment ( $P < 0.05$ ), and the peripheral blood levels of IL-4, IFN- $\gamma$ , TGF- $\beta$  and TNF- $\alpha$  in the EG were lower than those in the CG after treatment ( $P < 0.05$ ), indicating combined treatment could regulate the peripheral blood cytokine levels and suppress the inflammatory response (**Figure 2**).

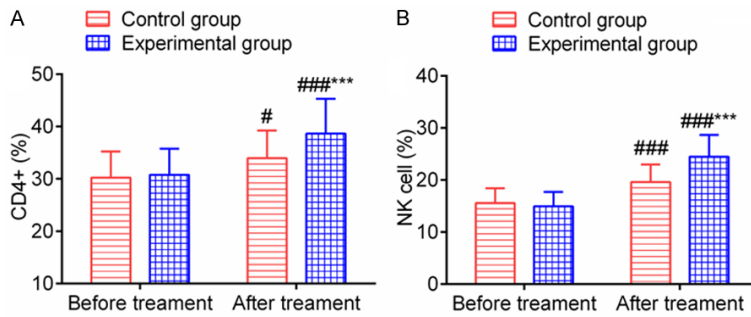
### Serum tumor markers

In order to observe the effect of DC-CIK immunotherapy combined with chemotherapy on tumor markers in the peripheral blood of patients, the changes of CA199, CA125, CYFRA211 and CEA levels in the peripheral blood of patients in the two groups were detected by ELISA. The results showed that there was no significant difference in the levels of CA199, CA125, CYFRA211 and CEA before treatment between the two groups ( $P > 0.05$ ). The levels of CA199, CA125, CYFRA211 and CEA in the peripheral blood in both groups after treatment were significantly lower than before treatment, and the levels of CA199, CA125, CYFRA211 and CEA in the EG were lower than those in the CG after treatment ( $P < 0.05$ ), suggesting that DC-CIK immunotherapy combined with chemotherapy could regulate the tumor marker levels and alleviate the disease (**Figure 3**).

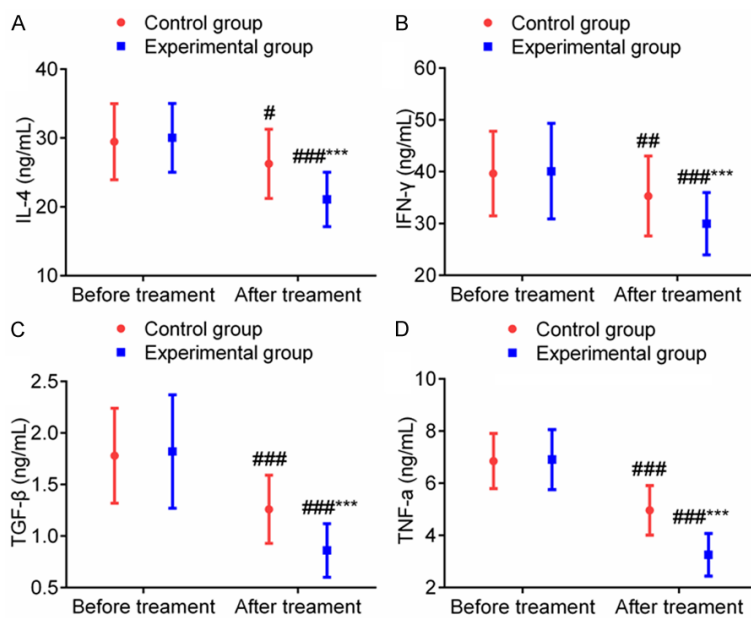
### Serum MMP-9, TIMP-1 and VEGF levels

In order to observe the effects of DC-CIK immunotherapy combined with chemotherapy on serum levels of MMP-9, TIMP-1 and VEGF, the changes of serum levels of MMP-9, TIMP-1 and VEGF in both groups of patients were detected by ELISA. The results showed that there was no significant difference in the levels of MMP-9, TIMP-1 and VEGF between the two groups before treatment ( $P > 0.05$ ). Serum levels of MMP-9, TIMP-1 and VEGF in both groups after treatment were lower than those before treat-

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**Figure 1.** Comparison of immune function. Note: A: CD4<sup>+</sup>; B: NK cells. Compared with the control group, \* $P < 0.05$ , \*\*\* $P < 0.001$ ; compared with the pre-treatment group, # $P < 0.05$ , ### $P < 0.001$ .



**Figure 2.** Comparison of peripheral blood cytokines. Note: A: IL-4; B: IFN-γ; C: TGF-β; D: TNF-α. Compared with the control group, \*\*\* $P < 0.001$ ; compared with the pre-treatment group, # $P < 0.05$ , ## $P < 0.01$ , ### $P < 0.001$ .

ment ( $P < 0.05$ ), and MMP-9, TIMP-1, and VEGF levels in the EG were lower than those in the CG after treatment ( $P < 0.05$ ), indicating that DC-CIK immunotherapy combined with conventional chemotherapy could inhibit tumor invasion and metastasis (Figure 4).

### Major adverse reactions

The major adverse reactions in the EG were not significantly different from those in the CG ( $P > 0.05$ ), indicating that DC-CIK immunotherapy combined with chemotherapy was safe (Table 3).

### Discussion

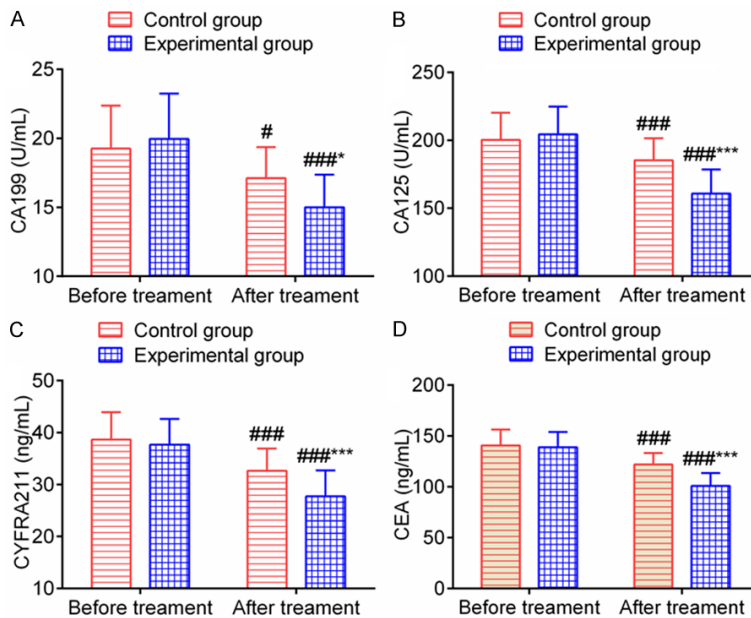
A Pemetrexed (or gemcitabine) + cisplatin chemotherapy regimen is commonly used in NSCLC patients to effectively reduce the number of cancer cells, but chemotherapeutic agents tend to induce T-cell proliferation and reduce cellular immunity [15]. Evidence has shown that lymphocytes that can recognize tumor cells in tumor patients, but they are weak numerically and functionally, resulting in a suppressed state of cellular immune function, which makes it difficult to control the progression of tumor [16]. Therefore, exogenous supplementation of immune cells can inhibit tumor growth and kill tumor cells by culturing these lymphocytes *in vitro*.

In this study, compared with the CG, the EG had a slightly higher control rate with no significant difference, but had significantly lower peripheral blood cytokine levels, and a significant improvement in T-lymphocytes, suggesting that DC-CIK immunotherapy combined with a routine chemotherapy regimen could control the disease, improve the immune function, and suppress the inflammatory response.

Han et al. [17] found a higher disease control rate with DC-CIK immunotherapy compared to the chemotherapy-only group, which is consistent with the results of the present study. The mechanism of DC-CIK immunotherapy may be attributed to the factors below: (1) NKG2D can promote cell proliferation and enhance cytotoxicity, while CIK cells express NKG2D receptors on the surface, which can exert cytotoxic activity and inhibit tumor cell proliferation by recognizing NKG2D ligands. (2) CIK cells can recognize tumor cells and promote the production of perforin and granzyme B to degrade target cells



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**Figure 3.** Comparison of serum tumor markers. Note: A: CA199; B: CA125; C: CYFRA211; D: CEA. Compared with the control group, \* $P < 0.05$ , \*\*\* $P < 0.001$ ; compared with the pre-treatment group, # $P < 0.05$ , ### $P < 0.001$ .

[18]. (3) CIK cells can secrete inflammatory factors such as IFN- $\gamma$  and TNF- $\alpha$ , inhibit TGF- $\beta$  and other immune factors, maintain Th1 and Th2 balance, activate the immune system, increase immune cell activity, express Fas molecules, inhibit cell proliferation, and promote apoptosis via the Fas/FasL pathway. (4) DC cells combined with antigen can activate initial CD4<sup>+</sup> T cells and maintain the balance of the body's immune function; DC cells can capture antigens on the surface of tumor cells, secrete many cellular immune factors, reduce the body's tolerance to tumors, and diminish damage to the body's cellular immune function due to chemotherapy. In addition, DC can have a direct or indirect effects on B cell proliferation and activate the humoral immune response [19, 20]. (5) DC and CIK are co-cultured and then infused back into the body to activate CIK cell killing sensitivity, promote proliferation and maturation of CIK cells, secrete and stimulate molecules and cytokines, thus enhancing tumor cell killing. (6) DC-CIK initiates the body's autoimmunity and promotes the proliferation of antigen-specific T cells and enhances the activities of killer cells [21].

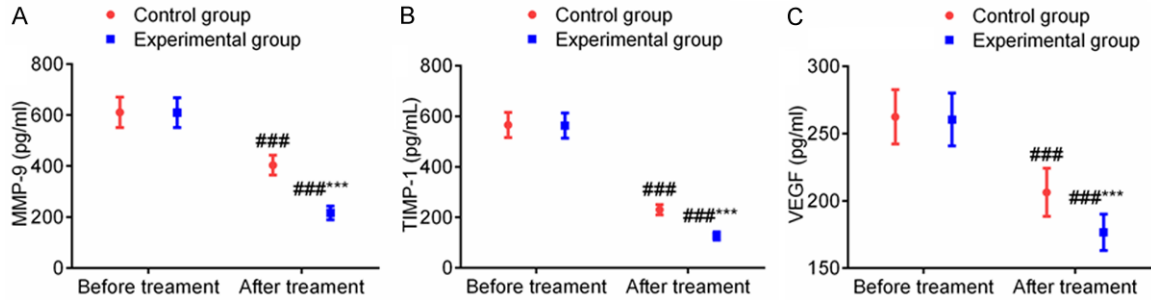
CA199 is one of the glycan-associated antigens and can be used as a key tumor marker in the diagnosis of lung cancer. Chen et al. [22] found

that CA199 was positively correlated with the staging of NSCLC patients. MMP-9 belongs to protein hydrolases that regulate cell-matrix and cell-cell adhesion and promotes neovascularization by degrading the extracellular matrix; it can induce VEGF and basic fibroblast growth factor, and accelerate the infiltration and metastasis of malignant tumors [23]. TIMP-1 specifically binds activated MMP-9, inhibits enzyme activation, and minimizes the proliferation and growth of tumor cells. Lim et al. [24] have confirmed that TIMP-1 and MMP-9 are highly expressed in the serum of NSCLC patients and may serve as candidate prognostic markers for NSCLC. In this study, the levels of CA199,

CA125, CYFRA211, CEA, MMP-9, TIMP-1, and VEGF in the EG were lower than those in the CG after treatment, indicating that DC-CIK immunotherapy combined with routine chemotherapy can regulate the serum tumor marker levels, alleviate the disease condition, and inhibit tumor invasion and metastasis. The results of a study by Zhong et al. [25] found that DC-CIK immunotherapy significantly reduced the incidence of adverse reactions such as leukopenia, probably because DC-CIK immunotherapy can target and kill tumor cells, improve patients' immune function without damaging healthy cells, thereby reducing the adverse effects of chemotherapy on postoperative adverse reactions. In this study, no significant difference was observed in the major adverse reactions such as leukopenia and thrombocytopenia between the two groups, which were inconsistent with the findings of the above study. The reason may be that the sample size included in this study is small.

In conclusion, DC-CIK immunotherapy combined with routine chemotherapy had significant curative efficacy in enhancing patients' cellular immune function, reducing inflammatory response, regulating tumor marker levels, and inhibiting tumor invasion and metastasis, without increasing adverse reactions. However,

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**Figure 4.** Comparison of serum MMP-9, TIMP-1 and VEGF levels between the two groups. Note: A: MMP-9; B: TIMP-1; C: VEGF. Compared with the control group, \*\*\* $P < 0.001$ ; compared with the pre-treatment group, #### $P < 0.001$ .

**Table 3.** Comparison of major adverse reactions [n (%)]

Group	Leukopenia	Thrombocytopenia	Gastrointestinal reactions	Bone marrow suppression
Control group (n=30)	5 (16.67)	7 (23.33)	8 (26.67)	3 (10.00)
Experimental group (n=30)	2 (6.67)	3 (10.00)	4 (13.33)	1 (3.33)
$\chi^2$	0.647	1.920	1.667	0.268
$P$	0.421	0.166	0.197	0.605

there is no uniform standard for the timing of DC-CIK application, culture time and method, and dose, which will be improved in future studies.

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### Disclosure of conflict of interest

None.

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