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ORIGINAL ARTICLE

Clinical efficacy analysis of dendritic cell-cytokine induced killer cell immunotherapy combined with paclitaxel-cisplatin chemotherapy in patients with advanced ovarian cancer

Yue Gao[1], Yafei Hao[2], Yuanyuan Jia[3]

[1]Department of Obstetrics and Gynecology, The Affiliated Huai'an Hospital of Xuzhou Medical University and The Second People's Hospital of Huai'an, Huai'an, China. [2]Department of Gynecology, Taian Central Hospital, Taian, China. [3]Oncology Department of Integrated Traditional Chinese and Western Medicine, The Affiliated Huai'an Hospital of Xuzhou Medical University and The Second People's Hospital of Huai'an, Huai'an, China.

Summary

Purpose: *To explore the efficacy and safety of dendritic cell-cytokine induced killer cell (DC-CIK) immunotherapy combined with paclitaxel-cisplatin chemotherapy in the treatment of advanced ovarian cancer.*

Methods: *Patients with advanced ovarian cancer formed the Chemotherapy group (paclitaxel-cisplatin, n=68) and the other 68 patients formed the DC-CIK group (DC-CIK + paclitaxel-cisplatin, n=68). The short-term efficacy and changes in the levels of immune function indexes, serum CD133 and DEAD-box helicase 4 (DDX4) were analyzed.*

Results: *Both overall response rate (ORR) and disease control rate (DCR) in the DC-CIK group were significantly better than those in the Chemotherapy group. After treatment, the proportions of $CD3^+$ T lymphocytes, $CD3^+$ $CD4^+$ T lymphocytes and NK cells and the CD4/CD8 ratio were evidently higher, while the proportion of $CD4^+$ $CD25^+$ T lymphocytes was evidently lower in the DC-CIK group than those in the Chemotherapy group. After treatment, the levels of basic fibroblast growth factor (bFGF), carbohydrate antigen 19-9 (CA19-9), CA125, human epididymis protein 4 (HE4), cytokeratin 19 fragment antigen 21-1 (CYFRA21-1), DDX4 and CD133 markedly declined in the two groups, and they were markedly lower in the DC-CIK group than in the Chemotherapy group. At 1 month after treatment, the score of emotional functioning in function module of QLQ-C30 scale was greatly higher in the DC-CIK group than that in the Chemotherapy group, while the score of nausea and vomiting in symptom module was greatly lower in the DC-CIK group than that in the Chemotherapy group. The follow-up analysis showed that the overall survival (OS) rate in the DC-CIK group was remarkably superior than in the Chemotherapy group.*

Conclusions: *DC-CIK immunotherapy combined with paclitaxel-cisplatin chemotherapy can greatly improve the clinical efficacy, enhance the immune function, reduce the levels of serum tumor markers, raise the quality of life and prolong the survival in patients with advanced ovarian cancer.*

Key words: *dendritic cell-cytokine induced killer cells, advanced ovarian cancer, cellular immunotherapy, efficacy*

Introduction

Ovarian cancer is one of the three major malignant tumors of the female reproductive system, and its morbidity rate ranks 6th among common female tumors in the world and is 6.0/100,000 in China currently, but its mortality rate is the highest among gynecological malignancies, seriously affecting women's life health and life [1,2]. In practice, ovarian cancer is still mainly treated with surgery, combined with radiotherapy and chemotherapy, but it is difficult to excise the tu-

Corresponding author: Yuanyuan Jia, MM. Oncology Department of Integrated Traditional Chinese and Western Medicine. The Affiliated Huai'an Hospital of Xuzhou Medical University and The Second People's Hospital of Huai'an, No.62,Huaihai South Rd, Qingjiangpu District, Huai'an, Jiangsu 223002, China.
Tel: +86 015189653723, Email: huagaxing19750113@163.com
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mor *via* primary cytoreductive surgery for most patients with advanced disease, and the effect of radiotherapy and chemotherapy is not significant [3]. As a new treatment means, tumor immunotherapy has attracted increasing attention. Dendritic cell-cytokine induced killer cell (DC-CIK) is a novel immunotherapy for malignant tumors. It has been reported that DC-CIK can enhance the immunity and improve the quality of life, with small side effects, and better tolerance [4-6]. Dendritic cells (DCs) are powerful professional antigen-presenting cells and one of the most effective ways to stimulate the immune system to resist cancer cell invasion. Cytokine induced killer cells (CIKs) have advantages such as potent anti-tumor activity of T lymphocytes and restricted tumor-killing activity of non-major histocompatibility complexes. DCs combined with CIKs are characterized by rapid proliferation, high tumor-killing activity and broad tumor-killing spectrum [7-9].

In the present study, the clinical efficacy and safety of DC-CIK immunotherapy combined with paclitaxel-cisplatin chemotherapy were explored in the treatment of advanced ovarian cancer, and its effect on the patients' immune function was analyzed, so as to provide a stronger basis for the development of clinical therapeutic regimens for such patients.

Methods

General data

A total of 136 patients with advanced ovarian cancer treated in our hospital were collected.

Inclusion criteria: 1) patients diagnosed with stage IV ovarian cancer *via* pathological examination and the International Federation of Gynecology and Obstetrics (FIGO 2004) surgicopathological staging criteria; 2) those with an expected survival time >6 months; 3) those with normal hematopoietic system, liver, kidney and heart functions; 4) those with a Karnofsky performance scale score ≥60 points; and 5) those without undergoing cellular immunotherapy before.

Exclusion criteria: 1) patients with severe heart, liver or kidney diseases or mental diseases; 2) those complicated with other malignant tumors; or 3) those with chronic or acute infectious diseases, or autoimmune diseases.

According to different treatment methods, the patients were divided into paclitaxel-cisplatin chemotherapy group (Chemotherapy group, n=68) and DC-CIK immunotherapy+paclitaxel-cisplatin chemotherapy group (DC-CIK group, n=68). The patient age was 55.56±8.95 years, and their baseline data in both groups before treatment had no statistically significant differences (p>0.05) (Table 1). This study was approved by the Ethics Committee of the Second People's Hospital of Huai'an, and all patients enrolled adhered to the *Declaration of Helsinki* and signed the informed consent.

Table 1. Baseline demographic and clinical characteristics of the studied patients

Parameters	*DC-CIK group (n=68)* *n (%)*	*Chemotherapy group (n=68)* *n (%)*	*p value*
Age, years	54.45±8.73	56.11±8.89	0.274
Histology			0.516
Serous cystadenocarcinoma	42 (61.8)	37 (54.4)	
Mucinous cystadenocarcinoma	19 (27.9)	17 (25.0)	
Endometrioid carcinoma	5 (7.4)	8 (11.8)	
Clear cell carcinoma	1 (1.5)	4 (5.9)	
Mixed epithelial carcinoma	1 (1.5)	2 (2.9)	
Differentiation grade			0.244
High	11 (16.2)	19 (27.9)	
Moderate	33 (48.5)	27 (39.7)	
Low	24 (35.3)	22 (32.4)	
TNM stage			0.379
IIIA	13 (19.1)	10 (14.7)	
IIIB	35 (51.5)	29 (42.6)	
IIIC	9 (13.2)	16 (23.5)	
IV	11 (16.2)	13 (19.1)	
KPS score			0.469
80-90	25 (36.8)	21 (30.9)	
60-80	43 (63.2)	47 (69.1)	

DC-CIK: dendritic cell-cytokine induced killer cells; TNM: tumor, lymph node, metastasis; KPS: Karnofsky performance status.

Treatment methods

In the Chemotherapy group, conventional TC chemotherapy (paclitaxel+carboplatin) was administered: Paclitaxel (175 mg/m^2) and cisplatin (75 mg/m^2) were intravenously injected on the 1st day of each cycle. In the DC-CIK group, DC-CIK immunotherapy combined with TC chemotherapy was administered: On day 1 before TC chemotherapy, DC-CIKs cultured by the peripheral blood were used for treatment. The treatment lasted for 3 cycles (21 days as 1 cycle) in both groups.

DC-CIK immunotherapy: 50 mL of peripheral blood was drawn from each patient 1 week before treatment, and DC-CIKs were prepared. After centrifugation, the plasma was taken out, diluted with normal saline and Dulbecco's Modified Eagle's Medium (DMEM). Then the mononuclear cells in the boundary layer were collected, washed with DMEM, suspended at a certain concentration, added with recombinant human interferon-γ, and cultured in an incubator with 50 mL/L CO_2 at 37°C. Two days later, the cluster of differentiation 3 (CD3) and recombinant human interleukin-2 (rhIL-2) culture medium was added and replaced every 3 days, and rhIL-2 culture medium was supplemented. After culture for about 1 week, the mixture was infused at the intermission of chemotherapy. After 3 cycles (21 days as 1 cycle), the efficacy was evaluated.

Observation indexes

Short-term efficacy: The short-term efficacy was evaluated based on the Response Evaluation Criteria In Solid Tumors (RECIST). Complete response (CR): All lesions disappear for more than 4 weeks. Partial response (PR): The product of two maximum vertical diameters of lesions declines by >50%. Stable disease (SD): The lesions shrink by <50% or have no changes. Progressive disease (PD): There are new lesions. Overall response rate (ORR) = (CR+PR)/total cases × 100%, and disease control rate (DCR) = (CR +PR+SD)/total cases × 100%.

Immunological indexes: On day 1 before the first course of chemotherapy and day 1 before the last course of chemotherapy, 3 mL of peripheral venous blood were drawn from patients. Then, the total T lymphocytes (CD3$^+$), helper T lymphocytes (CD3$^+$ CD4$^+$), immune state (CD4/CD8 ratio), regulatory T lymphocytes (CD4$^+$ CD25$^+$) and natural killer (NK) cells were detected using an FC500 flow cytometer (Beckman Coulter, USA).

The levels of human epididymis protein 4 (HE4), basic fibroblast growth factor (bFGF), carbohydrate antigen 125 (CA125), CA19.9, cytokeratin 19 fragment antigen 21-1 (CYFRA21-1), CD133 and DEAD-box helicase 4 (DDX4) and the incidence of adverse reactions were compared between the two groups before and after treatment. HE4 and CYFRA21-1 were detected *via* electrochemiluminescence immunoassay, and CA125, CA19.9, bFGF, CD133 and DDX4 were detected *via* enzyme-linked immunosorbent assay (ELISA).

One month after treatment, the quality of life of patients was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 scale, and the results were converted into 0-100 points based on the EORTC scoring guide. The higher scores of the function and total modules corresponded to the higher quality of life, while the higher score of the symptom module indicated the lower quality of life.

The patients were followed up once every 3 months within 2 years after treatment, and once every 6 months after 2 years. The survival time of patients was recorded, and those lost to follow-up were considered to be censored from the date of loss.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean±standard deviation, and t-test was performed for intergroup comparison. Chi square test or Fisher exact probability test were performed for comparison of clinical data. T-test was used for the intragroup comparison of paired data of immunological indexes, and two-way analysis of variance (ANOVA) for the intergroup comparison. The short-term efficacy and adverse reactions were compared *via* one-way analysis of variance, and detected using Mann-Whitney U test. The Kaplan-Meier survival curves were plotted for survival analysis, and log-rank test was performed to detect differences between two groups. P<0.05 indicated statistically significant difference.

Table 2. Comparison of tumor response of patients in the two studied groups

Parameters	*DC-CIK group (n=68)* *n (%)*	*Chemotherapy group (n=68)* *n (%)*	*p value*
Complete response (CR)	12 (17.6)	6 (8.8)	
Partial response (PR)	31 (45.6)	24 (35.3)	
Stable disease (SD)	19 (27.9)	22 (32.4)	
Progressive disease (PD)	6 (8.8)	16 (23.5)	
ORR (CR + PR)	43 (63.2)	30 (44.1)	0.025
DCR (CR + PR+SD)	62 (91.2%)	52 (76.5%)	0.020

DC-CIK: dendritic cell-cytokine induced killer cells; ORR: Objective response rate; DCR: Disease control rate.

Results

Comparison of short-term efficacy

The efficacy of all patients was evaluated 1 month after treatment. In the DC-CIK group, there were 12 (17.6%) cases of CR, 31 (45.6%) cases of PR, 19 (27.9%) cases of SD and 6 (8.8%) cases of PD, and the ORR and DCR were 63.2% (43 cases) and 91.2% (62 cases), respectively. In the Chemotherapy group, there were 6 (8.8%) cases of CR, 24 (35.3%) cases of PR, 22 (32.4%) cases of SD and 16 (23.5%) cases of PD, and the ORR and DCR were 44.1% (30 cases) and 76.5% (52 cases), respectively. It can be seen that both ORR and DCR in the DC-CIK group were significantly better than those in the Chemotherapy group, showing statistically significant differences (p=0.025, p=0.020) (Table 2).

Table 3. Comparison of immunological indicators of patients in the two studied groups

	DC-CIK group (n=68)	*Chemotherapy group (n=68)*	*p value*
$CD3^+$ T cell (%)			
Pretreatment	51.07±10.13	49.38±9.40	0.315
Posttreatment	61.61±13.63	52.32±11.14	0.001
$CD3^+CD4^+$ T cell (%)			
Pretreatment	30.13±7.09	31.75±8.03	0.215
Posttreatment	40.51±7.47	32.88±8.08	0.001
$CD4^+/CD8^+$ ratio			
Pretreatment	0.97±0.14	1.01±0.16	0.123
Posttreatment	1.34±0.19	1.05±0.14	0.001
$CD4^+$ $CD25^+$ cell (%)			
Pretreatment	11.89±3.20	12.46±3.19	0.300
Posttreatment	8.06±2.68	10.77±2.92	0.001
NK cell (%)			
Pretreatment	13.52±4.98	14.39±4.09	0.268
Posttreatment	24.19±6.22	15.59±5.49	0.001

DC-CIK: dendritic cell-cytokine induced killer

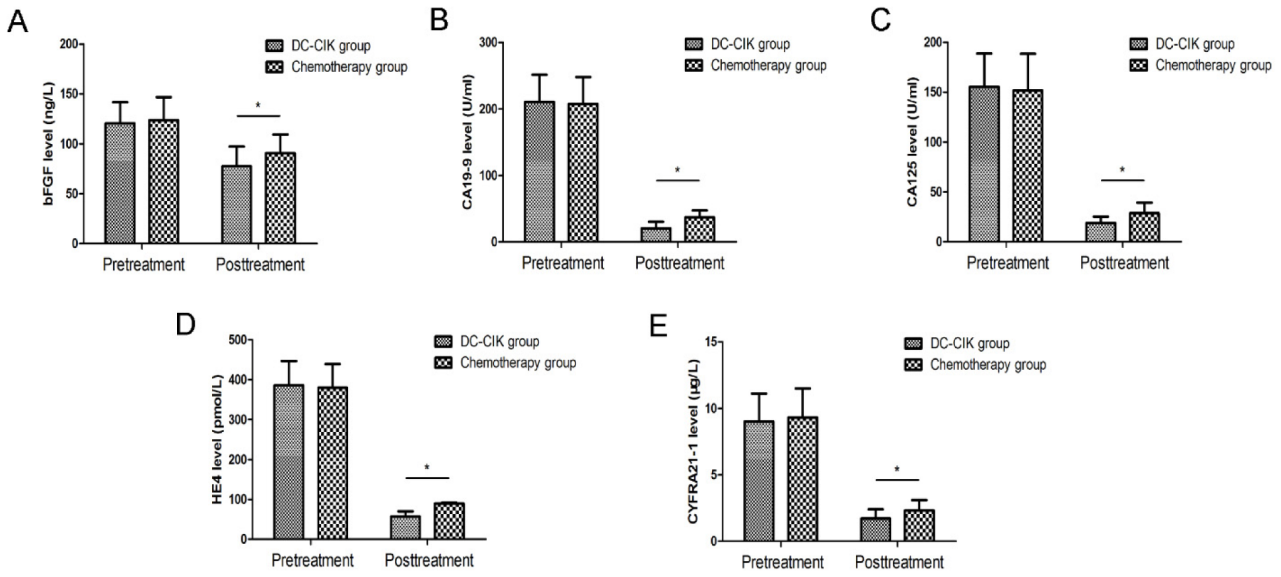

Figure 1. Comparison of pretreatment and posttreatment serum tumor markers of the studied patients. The difference between pretreatment serum bFGF **(A)**, CA19-9 (B), CA125 **(C)**, HE **(D)** and CYFRA21-1 **(E)** levels of patients in DC-CIK group and Chemotherapy group had no statistical significance (p>0.05). Serum bFGF **(A)**, CA19.9 **(B)**, CA125 **(C)**, HE **(D)** and CYFRA21-1 **(E)** levels of patients were significantly decreased after treatment (p>0.05). Posttreatment serum bFGF **(A)**, CA19-9 **(B)**, CA125 **(C)**, HE **(D)** and CYFRA21-1 **(E)** levels of patients in DC-CIK group were significantly lower than those of Chemotherapy group (*p<0.05).

Comparison of immunological indexes between the two groups before and after treatment

There were no statistically significant differences in the proportions of $CD3^+$ T lymphocytes, $CD3^+$ $CD4^+$ T lymphocytes, $CD4^+$ $CD25^+$ T lymphocytes and NK cells and the CD4/CD8 ratio between the two groups before treatment (p>0.05). After treatment, the proportions of $CD3^+$ T lymphocytes, $CD3^+$ $CD4^+$ T lymphocytes and NK cells and the CD4/CD8 ratio obviously rose, while the proportion of $CD4^+$ $CD25^+$ T lymphocytes obviously declined compared with those before treatment in the DC-CIK group (p<0.05). After treatment, the proportions of $CD3^+$ T lymphocytes, $CD3^+$ $CD4^+$ T lymphocytes and NK cells and the CD4/CD8 ratio were evidently higher, while the proportion of $CD4^+$ $CD25^+$ T lymphocytes was evidently lower in the DC-CIK group than those in the Chemotherapy group (p<0.001) (Table 3).

Comparison of serum tumor markers levels between the two groups before and after treatment

Before treatment, the levels of bFGF, CA19.9, CA125, HE4 and CYFRA21-1 had no statistically significant differences between the two groups (p=0.420, p=0.647, p=0.549, p=0.519, p=0.417). After treatment, the level of bFGF declined to 77.37±19.9 ng/L and 90.67±18.58 ng/L, the level of CA19-9 dropped to 20.69±9.89 U/mL and 36.96±10.10 U/mL, the level of CA125 was decreased to 18.84±6.56 U/mL and 28.57±10.67 U/mL, the level of HE4 declined to 57.15±12.92 pmol/L and 89.78±22.52 pmol/L, and the level of CYFRA21-1 was lowered to 1.7±0.7 μg/L and 2.3±0.8 μg/L, respectively, in the DC-CIK group and the Chemotherapy group. It can be seen that the levels of serum tumor markers were all markedly lower in the DC-CIK group compared to those in the Chemotherapy group (p<0.001) (Figure 1).

After treatment, the level of DDX4 was decreased from 152.65±29.42 U/mL and 156.88±28.93 U/mL to 16.86±4.03 U/mL and 35.23±5.60 U/mL, and the level of CD133 was decreased from 147.47±31.38 U/mL and 149.94±28.81 U/mL to 13.41±3.03 U/mL and 26.06±4.40 U/mL, respectively, in the DC-CIK group and the Chemotherapy group. The above results indicate that the levels of DDX4 and CD133 were remarkably lower in the DC-CIK group than those in the Chemotherapy group after treatment (p<0.001) (Figure 2).

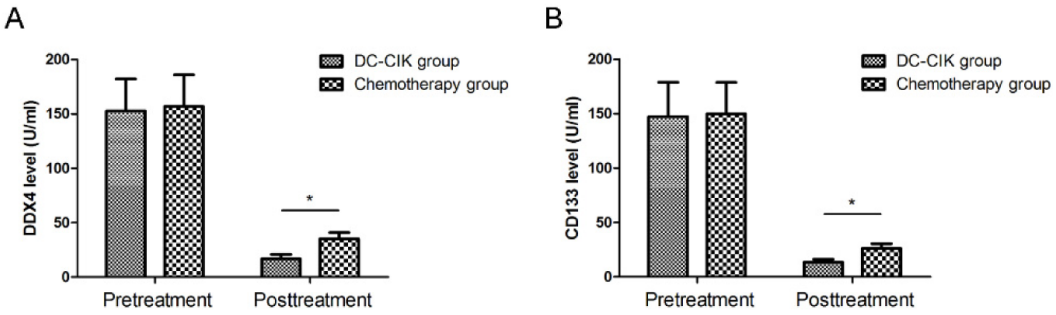

Figure 2. Comparison of pretreatment and posttreatment serum DDX4 **(A)** and CD133 **(B)** levels of the studied patients. The difference between pretreatment serum DDX4 **(A)** and CD133 **(B)** levels of patients in DC-CIK group and Chemotherapy group had no statistical significance (p>0.05). Serum DDX4 **(A)** and CD133 **(B)** levels of patients were significantly decreased after treatment (p<0.05). Posttreatment serum DDX4 **(A)** and CD133 **(B)** levels of patients in DC-CIK group were significantly lower than those of Chemotherapy group (*p<0.05).

Table 4. Comparison of adverse reactions of patients in the two studied groups

Parameters	*DC-CIK group (n=68)* *n (%)*	*Chemotherapy group (n=68)* *n (%)*	*p value*
Leukopenia	7 (13.2)	19 (27.9)	0.034
Anemia	10 (14.7)	13 (19.1)	0.493
Nausea and vomiting	21 (30.9)	16 (23.5)	0.335
Liver function damage	10 (14.7)	20 (29.4)	0.039
Renal function damage	11 (16.2)	14 (20.6)	0.507
Peripheral neurotoxicity	15 (22.1)	12 (17.6)	0.519

Table 5. Comparison of posttreatment EORTC-QLQ-C30 scale scores of the studied patients in two different groups

Complications	*DC-CIK group (n=68)*	*Chemotherapy group (n=68)*	*p value*
QLQ-C30			
Functioning scales			
Physical	98.62±20.41	98.08±19.19	0.874
Role	100±0	100±0	1.000
Emotional	93.73±14.74	84.96±15.49	0.001
Social	99.71±13.65	97.14±14.90	0.296
Cognitive	99.89±11.25	99.21±10.66	0.718
Symptom scales			
Appetite loss	48.73±22.15	50.02±20.54	0.725
Constipation	45.07±21.89	49.64±18.35	0.189
Dyspnea	1.14±2.98	1.30±3.09	0.759
Fatigue	24.35±13.26	25.94±11.02	0.448
Financial impact	63.58±19.45	67.63±18.33	0.214
Nausea and vomiting	25.88±12.48	31.03±13.93	0.025
Pain	37.39±8.75	40.03±9.73	0.099
Sleep disturbance	47.98±10.95	49.68±11.53	0.380

EORTC: European Organization for Research and Treatment of Cancer

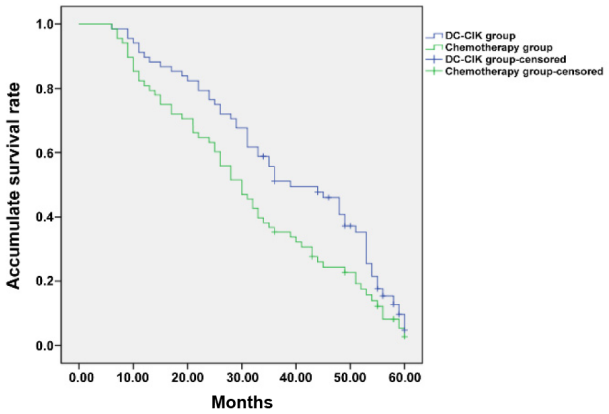

Figure 3. Kaplan-Meier survival curves of advanced ovarian carcinoma patients. The overall survival rate of patients in the DC-CIK group was significantly higher than those of the Chemotherapy group (p=0.029).

Comparison of adverse reactions

During treatment, the main adverse reactions were leukopenia, anemia, nausea and vomiting, liver and renal function damage and peripheral neurotoxicity. The incidence rate of leukopenia and liver function damage was distinctly lower in the DC-CIK group than that in the Chemotherapy group, while that of other adverse reactions had no statistically significant differences between the two groups (p>0.05) (Table 4).

Comparison of QLQ-C30 score between the two groups after treatment

The quality of life status was recorded *via* follow-up within 1 month after treatment. The score of emotional functioning in function module of QLQ-C30 scale was improved in the DC-CIK group, manifested as stable emotion, and less depression and rage, which was greatly higher than in the Chemotherapy group (93.73±14.74 points *vs.* 84.96±15.49 points, p<0.001). The score of nausea and vomiting in symptom module was greatly lower in the DC-CIK group than in the Chemotherapy group (25.88±12.48 points *vs.* 31.03±13.93 points, p=0.025). There were no statistically significant differences in other scores between the two groups (p>0.05) (Table 5).

Follow-up results of patient survival

All of the 136 patients were followed up for 6-60 months until December 2019. The median survival time was 36.9±6.5 months and 31.2±5.3 months, and the 3-year overall survival (OS) rate was 48.5% (33/68) and 35.3% (24/68), respectively, in the DC-CIK group and the Chemotherapy group. The survival curves of patients were plotted using the Kaplan-Meier method (Figure 3). The results of log-rank test showed that the OS rate in the DC-CIK group was remarkably superior to that in the Chemotherapy group, with a statistically significant difference (p=0.029).

Discussion

Ovarian cancer is a common malignant tumor of the female reproductive system. Due to no obvious early symptoms, about three-fourths of patients have been in mid-late stage at the time of diagnosis. Therefore, its mortality rate is the

highest among such malignancies [10]. After cytoreductive surgery and standard platinum-based chemotherapy, clinical response can be achieved, but the disease relapses quickly in most patients, with a 5-year survival rate of only about 30% [11]. DC-CIK immunotherapy is a novel adoptive immunotherapy, which can improve the immunity and prolong the survival of patients in the comprehensive therapy of lung cancer, gastric cancer and ovarian cancer, achieving good therapeutic effects [12-14]. In DC-CIK immunotherapy, DCs and CIKs of patients are co-cultured *in vitro* to increase the number and activity, and then they are infused to patients, so as to improve the body's tumor antigen recognition ability and tumor-killing ability, delay or reduce the tumor recurrence, and raise the tumor cure and survival rate of patients [15,16].

CA125, CA19.9 and HE4 are three commonly-used serum tumor markers for ovarian cancer. CA125 originates from glycoprotein antigen of epithelial ovarian cancer, which has great clinical significance for the diagnosis of this disease, and diagnostic sensitivity of more than 80% for serous subtype [17,18]. Studies have shown that CA125 is of great value for revealing postoperative recurrence and metastasis of ovarian cancer, and prediction of the sensitivity to chemotherapy drugs [19]. HE4 is a newly-discovered serum tumor marker for ovarian cancer in recent years. It is believed that HE4 combined with CA125 can increase the diagnostic rate of ovarian cancer in high-risk women [20]. DDX4 is present specifically in gonadal germ cells and highly expressed in ovarian cancer cells. CD133 has a similar expression pattern to that of DDX4, so it is also highly expressed in ovarian cancer tissues and acts as one of the important markers for tumor stem cells [21]. In this study, the results manifested that the short-term efficacy and ORR were obviously better in the DC-CIK group than in the Chemotherapy group. After treatment, the immunological indexes in the DC-CIK group were greatly improved compared with those before treatment, and they were superior to those in the Chemotherapy group ($p<0.001$). After treatment, the levels of bFGF, CA19.9, CA125, HE4, CYFRA21-1, DDX4 and CD133 evidently declined in both groups, while they were evidently lower in the DC-CIK group than in the Chemotherapy group ($p<0.001$). The above findings indicate that DC-CIK immunotherapy can enhance the immune function, improve the anti-tumor immune response, and significantly lower the levels of serum tumor markers in patients.

In this study it was found that the incidence of leukopenia and liver function damage was distinctly lower in the DC-CIK group than that in the Chemotherapy group, and the score of emotional functioning of QLQ-C30 scale markedly rose in the DC-CIK group. The possible mechanism of DC-CIK immunotherapy in improving adverse reactions and quality of life is as follows: Within a short period of time after treatment, a large number of immune cells will enter the patient's body and kill tumor cells to the utmost extent, so that the disease and corresponding adverse symptoms are controlled. Studies have shown that the degree of depression of patients is negatively correlated with the proportion of $CD4^+$ T cells. In this study, it was confirmed that DC-CIK combination therapy could raise the proportion of $CD4^+$ T cells, so patients in the DC-CIK group had a better emotional function. CIKs can secrete IL-2 with an analgesic effect. Therefore, DC-CIK combination therapy can relieve the painful symptoms and ameliorate the mental state of patients to a certain degree [22]. However, many patients complain that the effect of pain relief will last only within a few days after reinfusion.

This study is a single-center retrospective study, with a small sample size and short follow-up period. In the future, the results in this study need to be confirmed by more rigorous and scientific large-sample prospective multicenter randomized controlled studies, so as to provide references for selecting the therapeutic regimen for patients with advanced ovarian cancer.

Conclusions

DC-CIK immunotherapy combined with paclitaxel-cisplatin chemotherapy can greatly improve the clinical efficacy, enhance the immune function of patients, reduce the levels of serum tumor markers, raise the quality of life and prolong the survival of patients in the treatment of advanced ovarian cancer.

Conflict of interests

The authors declare no conflict of interests.

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