JBUON 2020; 25(5): 2364-2370
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Efficacy of dendritic cell-cytokine induced killer cells combined with concurrent chemoradiotherapy on locally advanced non-small cell lung cancer

Lin Tian[1], Wei Wang[2], Bin Yu[3], Guoxia Zhang[4]

[1]Department of Respirology, Affiliated Hospital of Changchun University of Traditional Chinese Medicine, Changchun 130021, China. [2]ICU, Affiliated Hospital of Changchun University of Traditional Chinese Medicine, Changchun 130021, China. [3]Department of Oncology-Hematology, Affiliated Hospital of Changchun University of Traditional Chinese Medicine, Changchun 130021, China. [4]Department of Oncology, Luohu District Chinese Medicine Hospital, Shenzhen 518000, China.

Summary

Purpose: *To explore the efficacy and safety of docetaxel/cisplatin concurrent chemoradiotherapy (CCRT) combined with dendritic cell-cytokine induced killer cell (DC-CIK) immunotherapy in the treatment of locally advanced non-small cell lung cancer (LANSCLC).*

Methods: *The clinical data of 142 LANSCLC patients treated in our hospital from March 2014 to March 2016 were retrospectively analyzed. 71 patients were treated with docetaxel/cisplatin CCRT (CCRT group), while the remaining 71 patients underwent CCRT combined with DC-CIK immunotherapy (DC-CIK group). The clinical data of all patients were collected, the short-term efficacy, the changes in serum immunological indexes and quality of life before and after treatment, and the incidence of adverse reactions were compared between the two groups, and the overall survival (OS) and progression-free survival (PFS) were recorded during the follow-up of patients.*

Results: *After treatment, the level of cluster of differentiation 3$^+$ ($CD3^+$) $CD4^+$ T lymphocytes, CD4/CD8 ratio and $CD56^+$ natural killer (NK) cell ratio significantly rose, while the level of $CD3^+$ $CD8^+$ T lymphocytes significantly declined in both groups compared with those before treatment. After treatment, the level of $CD3^+$ $CD4^+$ T lymphocytes, CD4/CD8 ratio and $CD56^+$ NK cell ratio were obviously higher, while the level of $CD3^+$ $CD8^+$ T lymphocytes was obviously lower in DC-CIK group than those in CCRT group. At 12 months after treatment, both Karnofsky performance scale (KPS) score and quality of life (QOL) score in DC-CIK group were evidently higher than those in CCRT group. In CCRT group and DC-CIK group, 1-year OS was 74.6% and 83.1%, and 1-year PFS was 70.4% and 73.2%, respectively. 2-year OS was 45.1% and 57.7%, and 2-year PFS was 38.0% and 46.5%), respectively. 3-year OS was 26.8% and 40.8%, and 3-year PFS was 15.5% and 22.5%, respectively. It can be seen that both OS and PFS in DC-CIK group were remarkably superior to those in CCRT group.*

Conclusion: *Docetaxel/cisplatin CCRT combined with DC-CIK can significantly enhance the cellular immunity, improve the long-term survival rate and raise the quality of life of LANSCLC patients, with tolerable adverse reactions.*

Key words: *dendritic cells, killer cells, non-small cell lung cancer, locally advanced, concurrent chemoradiotherapy, efficacy*

Introduction

Locally advanced non-small cell lung cancer (LANSCLC) patients refer to stage III in any one of N2, N3 and T4 except for T3N1M0 and malignant pleural effusion, accounting for about 45% in NSCLC patients, with poor clinical efficacy. The 5-year survival rate is 15-23% in stage IIIA patients and only 6-7% in stage IIIB patients, and the therapeutic regimens are complex and contro-

Corresponding author: Guoxia Zhang, MD. Department of Oncology, Luohu District Chinese Medicine Hospital, 16 Xiantong Rd, Luohu District, Shenzhen 518000, China.
Tel: +86 015338707007, Email: guoxia.1980@163.com
Received: 13/11/2019; Accepted: 08/01/2020

versial [1,2]. In recent years, several multicenter randomized studies have confirmed that concurrent chemoradiotherapy (CCRT) is superior to sequential chemoradiotherapy, the former of which, therefore, has become the standard treatment for LANSCLC [3-5].

An effective immune system is an important factor for preventing the recurrence and metastasis in LANSCLC patients. Dendritic cells (DCs) possess a strong effect of antigen presentation, which play an important role in the generation and mediation of immune mechanism in lung cancer patients. Cytokine-induced killer cells (CIKs) have a certain toxic effect on tumor cells [6]. The immunotherapy based on DCs and CIKs has a high success rate and little harm to human body [7]. Studies have pointed out that after co-incubation of DCs and CIKs, not only the expression of costimulatory molecules in DCs is elevated, but also the ability of antigen presentation, increase in CIKs and cytotoxicity are significantly enhanced [8]. The DC-CIK-based immunotherapy has been applied in the treatment of a variety of malignant tumors [9-12]. In this study, the clinical efficacy and safety of DC-CIK combined with docetaxel/cisplatin CCRT in the treatment of LANSCLC patients were explored.

Methods

General data

A total of 142 LANSCLC patients treated in our hospital from March 2014 to March 2016 were studied. Inclusion criteria: patients diagnosed with NSCLC via fiberoptic bronchoscopy, biopsy or cytology, those in stage IIIA and IIIB according to the criteria of the International Association for the Study of Lung Cancer in 2009 (7th edition), those with normal function in the hematopoietic system, liver, kidney and heart, those with Karnofsky performance scale (KPS) score ≥70 points, those aged ≤75 years old and treated with the first treatment without a history of radiotherapy and chemotherapy, and those with the measurable lesions ≥1.0 cm shown in spiral CT. Exclusion criteria: patients who were allergic to the treatment in this study, or those with severe diseases in the heart, liver or kidney, mental illness, chronic or acute infectious diseases, or autoimmune diseases. According to different treatments, patients were divided into docetaxel/cisplatin CCRT group (CCRT group, n=71) and CCRT combined with DC-CIK immunotherapy group (DC-CIK group, n=71). There were 81 males and 61 females with an average age of 60.86±10.95 years. The baseline data had no statistically significant differences between the two groups before treatment (Table 1, p>0.05). This study was approved by the Ethics Committee of Affiliated Hospital of Changchun University of Traditional Chinese Medicine. All patients enrolled adhered to the *Declaration of Helsinki* and signed the informed consent.

Therapeutic regimens

All patients underwent CCRT: Docetaxel was intravenously infused (75 mg/m^2) on 1 d, and cisplatin was intravenously infused (25 mg/m^2) on 1-3 d for a total of 4 cycles (28 d as 1 cycle). Vitamin B12 and folic acid were supplemented from 1 week before chemotherapy, and dexamethasone was taken orally (7.5 mg/time, twice/d) from 1 d before chemotherapy for 3 consecutive days for pre-desensitization. During treatment, the hemogram was reviewed at least twice every week. In case of myelosuppression above grade 2, the granulocyte-macrophage colony stimulating factor was applied, and the next cycle of chemotherapy was appropriately postponed if the recovery of hemogram was slow. Viana-600 linear accelerator with 6-MV X-ray was used in three-dimensional conformal intensity-modulated radiotherapy, and Eclipse

Table 1. Baseline characteristics of the studied patients

Characteristics	*CCRT group (N=71) n (%)*	*DC-CIK group (N=71) n (%)*	*p value*
Age (years)	60.4±11.3	61.8±10.9	0.454
Gender (Male/ Female)	38/33	43/28	0.498
Pathological type			0.750
Squamous cell carcinoma	26 (36.6)	29 (40.8)	
Adenocarcinoma	39 (54.9)	38 (53.5)	
Others	6 (8.5)	4 (5.6)	
Clinical stage			0.502
IIIA	39 (36.8)	35 (32.4)	
IIIB	32 (63.2)	36 (67.6)	
KPS score			0.615
80-90	37 (55.9)	34 (50)	
70-80	34 (44.1)	37 (50)	
QoL score	40.84±7.14	41.97±8.91	0.406

CCRT: Concurrent chemoradiotherapy; DC-CIK: Dendritic cell-cytokine induced killer; KPS: Karnofsky performance status; QoL: Quality of Life

treatment planning system (TPS) was used. The two lung V20 was ≤27%, the mean lung dose was ≤17 Gy, the maximum spinal cord dose was ≤45 Gy, and heart V50 was ≤50%. Prescribed dose: gross tumor volume (GTV) and GTV_{LN}: 64-70 Gy/28-30F, clinical target volume (CTV): 50-54 Gy/28-30F.

DC-CIK group: Blood was drawn to isolate the autologous peripheral blood mononuclear cells. 100 mL of serum was cultured in the Roswell Park Memorial Institute 1640 (RPMI 1640) complete medium (HyClone, South Logan, UT, USA), and the cell concentration was adjusted. The cytokines were complemented, and recombinant human tumor necrosis factor-α (TNF-α) was added to induce the maturation of DCs. The tumor cell antigen was prepared and CIKs were induced. The culture was taken to culture bacteria and fungi, and the mycoplasma, chlamydia and endotoxin were detected (criteria: pathogenic test negative, endotoxin <5 EU). About 1×10^{10} DC-CIKs were collected and cultured at 12-14 d, centrifuged at 500 g for 10 min, washed for 3 times, resuspended in 200 mL of normal saline, and supplemented with 2.5 mL of 20% human albumin. Then the mixture was intravenously infused back into the patients within 1 h. Whether adverse reactions such as fever, allergy and allergic reactions occurred was closely observed within 2-3 h after infusion. After 2 cycles of chemotherapy, DC-CIKs were infused back in the last 2 weeks at the intermission of chemotherapy twice a week for 4 times. The patients in DC-CIK group received 4 cycles of chemotherapy and 2 cycles of DC-CIK immunotherapy.

Observation indexes

Short-term efficacy: At 1 month after treatment, the short-term efficacy was evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The overall response rate (ORR) was calculated in both groups.

Immunological indexes: Before CCRT and at 1 month after treatment, the blood was drawn, and the cluster of differentiation 3^+ ($CD3^+$) $CD4^+$ and $CD3^+$ $CD8^+$ T lymphocytes, CD4/CD8 ratio and $CD56^+$ natural killer (NK) cell ratio were analyzed via flow cytometry, based on which the cellular immune function of patients was evaluated.

Adverse reactions: The acute radioactive reactions were evaluated according to the criteria of the Radiation Therapy Oncology Group, and the chemotherapy toxic reactions were evaluated based on the Common Terminology Criteria Adverse Events v3.0.

Quality of life: Before treatment and at 6 and 12 months after treatment, the KPS score and quality of life (QoL) score were assessed.

Survival condition: All patients were followed up once every 3 months within 2 years after treatment, and once every 6 months after 2 years through chest CT, brain MRI, and neck and abdominal color ultrasonography. The overall survival (OS) and progression-free survival (PFS) of patients were recorded. Those lost to follow-up were eliminated since the date of loss. OS refers to the time from enrollment to death due to any reason, and PFS refers to the time from treatment to progression of tumor in any way or death due to any reason.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. The measurement data were expressed as mean ± standard deviation. T-test was performed for the comparison between two groups, and x^2 test or Fisher's exact probability test for the comparison of clinical data. T-test was adopted for the intragroup comparison of immunological indexes, and two-way analysis of variance (ANOVA) for the intergroup comparison. The short-term efficacy and adverse reactions were compared through Mann-Whitney U test. In survival analysis, the Kaplan-Meier curves were plotted and log-rank test was performed to search for survival differences between two groups. $P<0.05$ suggested statistically significant difference.

Results

Comparison of short-term efficacy

The efficacy was evaluated in all patients at 1 month after treatment. In CCRT group, there were 20 cases (28.2%) of CR, 31 cases (43.7%) of PR, 18 cases (25.4%) of SD and 2 cases (2.8%) of PD, and the ORR was 71.8% (51/71). In DC-CIK group, there were 23 cases (32.4%) of CR, 36 cases (50.7%) of PR, 9 cases (12.7%) of SD and 3 cases (4.2%) of PD, and the ORR was 83.1% (59/71). The ORR had no statistically significant difference between the two groups (p=0.108) (Table 2).

Table 2. Clinical effective rates of the two studied groups

	CCRT group (N=71) n (%)	*DC-CIK group (N=71) n (%)*	*p value*
CR	20 (28.2)	23 (32.4)	
PR	31 (43.7)	36 (50.7)	
SD	18 (25.4)	9 (12.7)	
PD	2 (2.8)	3 (4.2)	
ORR	51 (71.8)	59 (83.1)	0.108

CCRT: Concurrent chemoradiotherapy; DC-CIK: Dendritic cell-cytokine induced killer; CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ORR: Objective response rate

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

After treatment, the level of $CD3^+$ $CD4^+$ T lymphocytes, CD4/CD8 ratio and $CD56^+$ NK cell ratio rose significantly, while the level of $CD3^+$ $CD8^+$ T lymphocytes declined significantly in both groups compared with those before treatment ($p<0.05$). The above indexes had statistically significant differences within groups before and after treatment ($p<0.05$), while they had no statistically significant differences between the two groups before treatment ($p>0.05$). After treatment, the level of $CD3^+$ $CD4^+$ T lymphocytes, CD4/CD8 ratio and $CD56^+$ NK cell ratio were obviously higher ($p<0.001$), while the level of $CD3^+$ $CD8^+$ T lymphocytes was obviously lower in DC-CIK group than those in CCRT group ($p=0.004$) (Table 3).

Comparison of KPS and QoL scores between the two groups

No statistically significant differences were found in KPS and QoL scores between the two groups before treatment and at 6 months after treatment ($p>0.05$). At 12 months after treatment, both KPS score and QoL score in DC-CIK group were evidently higher than those in CCRT group [(84.04±18.81) *vs.* (89.88±17.89), $p=0.040$; (45.74±9.69) *vs.* (50.36±8.29), $p=0.003$] (Figure 1).

Comparison of adverse reactions

The main adverse reactions during treatment were fever, nausea and vomiting, myelosuppression, radiation pneumonitis and radiation esophagitis (Table 4). There was no statistically significant

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

	CCRT group (N=71)	*DC-CIK group (N=71)*	*p value*
$CD3^+CD4^+$ T cell (%)			
Pretreatment	24.67±3.13	24.78±3.30	0.839
Posttreatment	26.64±3.68	28.92±3.44	0.001
$CD3^+CD8^+$ T cell (%)			
Pretreatment	28.11±3.09	28.55±3.33	0.416
Posttreatment	26.41±3.43	24.83±3.02	0.004
CD4/CD8 ratio			
Pretreatment	0.54±0.18	0.53±0.17	0.734
Posttreatment	0.74±0.19	0.91±0.24	0.001
$CD56^+$ NK cell (%)			
Pretreatment	6.22±1.98	6.39±1.90	0.603
Posttreatment	8.11±2.02	10.19±2.49	0.001

CCRT: Concurrent chemoradiotherapy; DC-CIK: Dendritic cell-cytokine induced killer

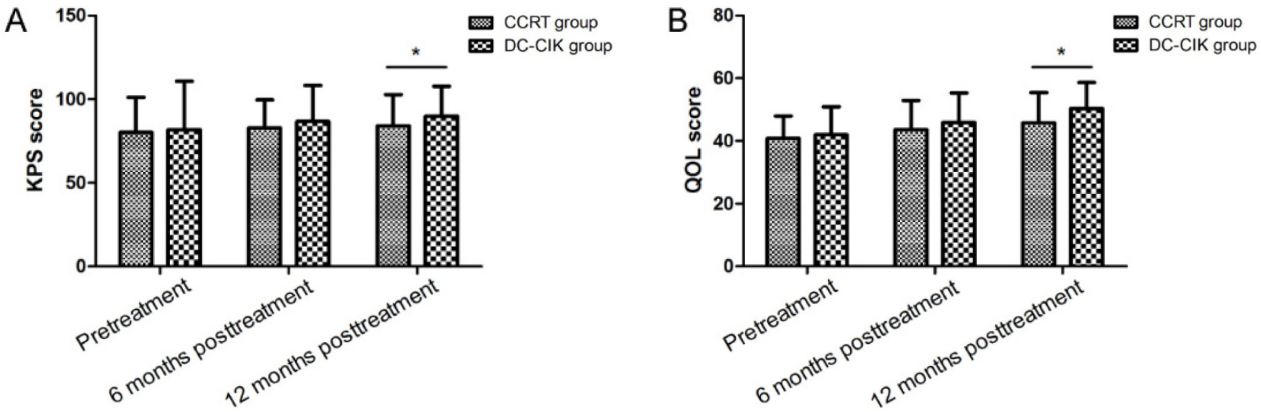

Figure 1. Comparison of KPS score and QoL score before and after treatment. **A:** Pretreatment and 6 months posttreatment KPS score of patients in CCRT group and DC-CIK group were 80.21±20.93, 81.82±28.90 and 82.78±16.83, 86.68±21.50 respectively, without significant differences between these two groups ($p=0.704$, $p=0.231$). 12 months posttreatment KPS score of patients in DC-CIK group was significantly higher than that of CCRT group [(89.88±17.89) *vs.* (84.04±18.81), $p=0.040$]. **B:** Pretreatment and 6 months posttreatment QoL score of patients in CCRT group and DC-CIK group were 40.84±7.14, 41.97±8.91, 43.65±9.23 and 45.88±9.45 respectively, without significant differences between these two groups ($p=0.406$, $p=0.157$). 12 months posttreatment QoL score of patients in DC-CIK group was significantly higher than that of CCRT group [(50.36±8.29) *vs.* (45.74±9.69), $p=0.003$].

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

Parameters	*CCRT group (n=71)*		*DC-CIK group (n=71)*		*p value*
	Grade I-II n (%)	*Grade III-IV n (%)*	*Grade I-II n (%)*	*Grade III-IV n (%)*	
Fever	10 (14.1)	0 (0)	13 (18.3)	0 (0)	0.649
Nausea / Vomiting	26 (36.6)	0 (0)	20 (28.2)	0 (0)	0.370
Bone marrow suppression	11 (15.5)	2 (2.8)	8 (11.3)	1 (1.4)	0.487
Radiation pneumonia	4 (5.6)	0 (0)	6 (8.5)	0 (0)	0.745
Radiation esophagitis	3 (4.2)	0 (0)	2 (2.8)	0 (0)	1.000

CCRT: Concurrent chemoradiotherapy; DC-CIK: Dendritic cell-cytokine induced killer

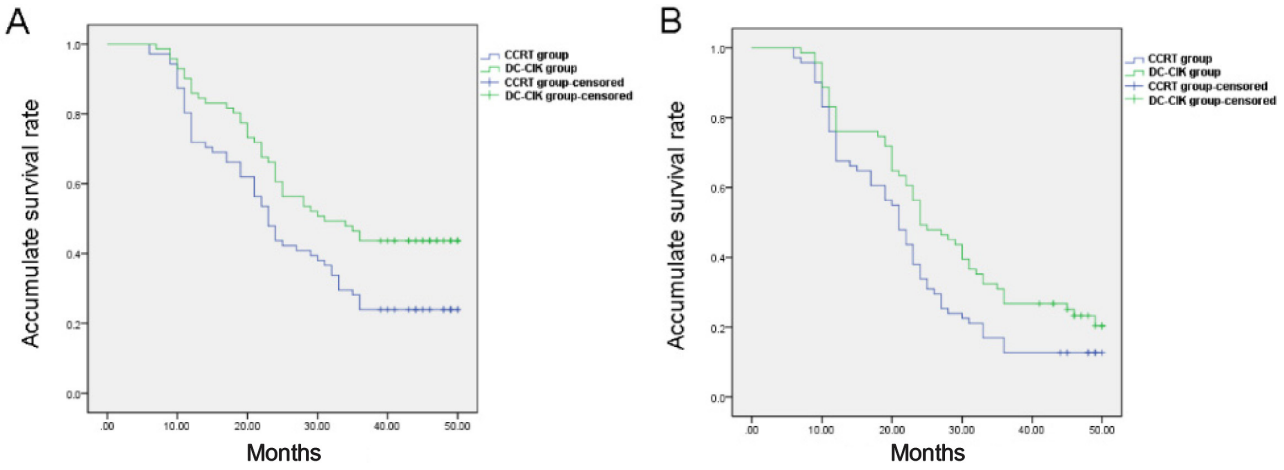

Figure 2. Kaplan-Meier survival curves of patients in CCRT group and DC-CIK group. **A:** The overall survival rate of patients in DC-CIK group was significantly higher than that of CCRT group (p=0.011). **B:** The progression-free survival rate of patients in DC-CIK group was significantly higher than that of CCRT group (p=0.026).

difference in the incidence of treatment-related adverse reactions between the two groups (p>0.05).

Follow-up results

All of 142 patients were followed up for 6-50 months until June 2019. In CCRT group and DC-CIK group, 1-year OS was 74.6% (53/71) and 83.1% (59/71), and 1-year PFS was 70.4% (50/71) and 73.2% (52/71), respectively. Two-year OS was 45.1% (32/71) and 57.7% (41/71), and 2-year PFS was 38.0% (27/71) and 46.5% (33/71), respectively. Three-year OS was 26.8% (19/71) and 40.8% (29/71), and 3-year PFS was 15.5% (11/71) and 22.5% (16/71), respectively. The survival curves of patients were plotted using the Kaplan-Meier method (Figure 2). According to the log-rank test, both OS and PFS in DC-CIK group were remarkably superior to those in CCRT group, displaying statistically significant differences (p=0.011, p=0.026).

Discussion

When diagnosed, 30-40% of NSCLC are in the locally advanced stage, and surgical resection becomes difficult to be performed. CCRT has become the standard treatment for LANSCLC [13]. Although the 5-year survival rate of LANCSLC is increased by CCRT to 15%, its overall efficacy remains poor, so it is important to search for better treatment means and combinations. DC-CIK combination therapy is one of the most commonly used immunotherapies to improve immunity and resist tumor. DCs and CIKs are two kinds of cells for clinical anti-tumor immunotherapy, the former of which are the strongest antigen presenting cells highly and specifically expressed in major histocompatibility complex (MHC) class I and II antigens, and the latter of which are cells with a strong killing effect, induced by various cytokines *in vitro* in human peripheral blood mononuclear cells [14]. The co-culture of DCs and CIKs can promote not only the maturation of DCs, but also the proliferation of CIKs, in which case the antigen-presenting ability of DCs and activity of CIKs are also evidently enhanced [15,16]. The cell-mediated adoptive immunotherapy DC-CIK has become one of the important means of adjuvant therapy after surgery and chemoradiotherapy in cancer patients, and it

has achieved good effects in improving immune function and eliminating residual lesions, which has been confirmed in the clinical test of various tumors [17,18].

In this study, the ORR was 71.8% in CCRT group and 83.1% in DC-CIK group, showing no statistically significant difference between the two groups (p=0.108). A number of studies has demonstrated that cancer patients suffer from severe defects in cellular immune function, manifested as the decline in $CD3^+$ $CD4^+$ T lymphocytes, $CD4^+$/$CD8^+$ ratio, killing ability of CIKs and $CD56^+$ NK cells, and the increase in $CD3^+$ $CD8^+$ T lymphocytes [19,20]. In this study, the cellular immune function was compared between the two groups, and it was confirmed that DC-CIK group had significantly enhanced cellular immune function compared with CCRT group, thereby enhancing anti-tumor immunity, effectively eliminating residual or small metastatic lesions, and preventing tumor recurrence and metastasis. There will be initial progression or even new lesions before remission of tumor in immunotherapy, and this is because lymphocytes may expand the tumor when infiltrating into it. Therefore, it is improper to evaluate the efficacy of immunotherapy according to the conventional RECIST, and it is needed to establish the evaluation system for the efficacy of immunotherapy [21]. It also shows that compared with the direct killing effect of cytotoxic drugs on tumor cells, the response in immunotherapy is an indirect dynamic process [22]. In this study, the fact that there was no statistically significant difference in the ORR between the two groups may be related to the above reasons. In this study, the effects of the two therapeutic regimens on KPS score and QoL score were compared, and it was observed that both scores in DC-CIK group were evidently higher than those in CCRT group at 12 months after treatment. Besides, DC-CIK group had milder adverse reactions of immunotherapy, and the incidence of adverse reactions had no obvious difference between the two groups, and they were tolerable.

According to a number of studies, DC-CIK combined with chemotherapy, targeted therapy or ablation therapy can prolong the survival of patients with LANSCLC (stage IIIB-IV), which plays an important role in initial and maintenance treatment [23-25]. In this study, both OS and PFS in DC-CIK group were remarkably superior to those in CCRT group, displaying statistically significant differences (p=0.011, p=0.026), consistent with previous literature reports. Zhong et al [24] conducted a clinical research on different frequencies of DC-CIK immunotherapy after chemotherapy for stage IIIB-IV LANSCLC, in which 60 patients were randomly divided into control group (treated with 4 cycles of NP routine chemotherapy and then 2 cycles of DC-CIK therapy, 30 d as 1 cycle) and observation group (treated with 4 cycles of NP routine chemotherapy and then DC-CIK therapy for >2 cycles), and they found that the 1-, 2- and 3-year OS in control group and observation group was 56.7%, 13.3% and 6.7%, and 63.3%, 30.0% and 23.3%, respectively, and the time to progression (TTP) was 6.2 months and 7.3 months, respectively, showing statistically significant differences. It can be seen that the DC-CIK therapy for >2 cycles can better raise OS and prolong TTP [24]. In this study, 2 cycles of DC-CIK therapy were performed at the intermission of chemotherapy, but whether the higher frequency of DC-CIK therapy can further improve the efficacy still needs further clinical research.

As a single-center retrospective study, there were certain limitations in this study. For example, the sample size was not large enough, the follow-up time was short, and the objects of study were LANSCLC patients with large tumor burden and a low level of basal immunity. In the future, the results in this study need to be confirmed by more rigorous and scientific large-sample prospective multicenter randomized controlled tests, so as to provide references for selecting the therapeutic regimen for LANSCLC.

Conclusions

Docetaxel/cisplatin CCRT combined with DC-CIK can significantly enhance the cellular immunity, improve the long-term survival rate and raise the QoL of LANSCLC patients, with tolerable adverse reactions.

Conflict of interests

The authors declare no conflict of interests.

References

1. Postmus PE, Kerr KM, Oudkerk M et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:v1-v21.

2. Puri S, Shafique M, Gray JE. Immune Checkpoint Inhibitors in Early-Stage and Locally Advanced Non-Small Cell Lung Cancer. Curr Treat Options Oncol 2018;19:39.
3. Govindan R, Bogart J, Stinchcombe T et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. J Clin Oncol 2011;29:3120-5.
4. Yu Y, Zhang X, Tian H, Zhang Z, Tian Y. Knockdown of long non-coding RNA HOTAIR increases cisplatin sensitivity in ovarian cancer by inhibiting cisplatin-induced autophagy. J BUON 2018;23:1396-1401.
5. Jie WX, Miao K, Luo Y et al. Randomized controlled trial of endostar combined with cisplatin/ pemetrexed chemotherapy for elderly patients with advanced malignant pleural effusion of lung adenocarcinoma. J BUON 2018;23:92-7.
6. Gunzer M, Janich S, Varga G, Grabbe S. Dendritic cells and tumor immunity. Semin Immunol 2001;13:291-302.
7. Constantino J, Gomes C, Falcao A, Neves BM, Cruz MT. Dendritic cell-based immunotherapy: a basic review and recent advances. Immunol Res 2017;65:798-810.
8. Wang S, Wang Z. Efficacy and safety of dendritic cells co-cultured with cytokine-induced killer cells immunotherapy for non-small-cell lung cancer. Int Immunopharmacol 2015;28:22-8.
9. Shi SB, Ma TH, Li CH, Tang XY. Effect of maintenance therapy with dendritic cells: cytokine-induced killer cells in patients with advanced non-small cell lung cancer. Tumori 2012;98:314-9.
10. Zhan HL, Gao X, Pu XY et al. A randomized controlled trial of postoperative tumor lysate-pulsed dendritic cells and cytokine-induced killer cells immunotherapy in patients with localized and locally advanced renal cell carcinoma. Chin Med J (Engl) 2012;125:3771-7.
11. Wang X, Tang S, Cui X et al. Cytokine-induced killer cell/dendritic cell-cytokine-induced killer cell immunotherapy for the postoperative treatment of gastric cancer: A systematic review and meta-analysis. Medicine (Baltimore) 2018;97:e12230.
12. Jiang N, Qiao G, Wang X et al. Dendritic Cell/Cytokine-Induced Killer Cell Immunotherapy Combined with S-1 in Patients with Advanced Pancreatic Cancer: A Prospective Study. Clin Cancer Res 2017;23:5066-73.
13. Arbour KC, Riely GJ. Systemic Therapy for Locally Advanced and Metastatic Non-Small Cell Lung Cancer: A Review. JAMA 2019;322:764-74.
14. Yamaguchi Y, Ohshita A, Kawabuchi Y et al. Adoptive immunotherapy of cancer using activated autologous lymphocytes--current status and new strategies. Hum Cell 2003;16:183-9.
15. Yang T, Zhang W, Wang L et al. Co-culture of dendritic cells and cytokine-induced killer cells effectively suppresses liver cancer stem cell growth by inhibiting pathways in the immune system. BMC Cancer 2018;18:984.
16. Su Y, Yang Y, Ma Y et al. The Efficacy and Safety of Dendritic Cells Co-Cultured with Cytokine-Induced Killer Cell Therapy in Combination with TACE-Predominant Minimally-Invasive Treatment for Hepatocellular Carcinoma: a Meta-Analysis. Clin Lab 2016;62:599-608.
17. Wang D, Zhang B, Gao H et al. Clinical research of genetically modified dendritic cells in combination with cytokine-induced killer cell treatment in advanced renal cancer. BMC Cancer 2014;14:251.
18. Gao D, Li C, Xie X et al. Autologous tumor lysate-pulsed dendritic cell immunotherapy with cytokine-induced killer cells improves survival in gastric and colorectal cancer patients. PLoS One 2014;9:e93886.
19. Gardner A, Ruffell B. Dendritic Cells and Cancer Immunity. Trends Immunol 2016;37:855-65.
20. Mohsenzadegan M, Peng RW, Roudi R. Dendritic cell/cytokine-induced killer cell-based immunotherapy in lung cancer: What we know and future landscape. J Cell Physiol 2020;235:74-86.
21. Weber J. Ipilimumab: controversies in its development, utility and autoimmune adverse events. Cancer Immunol Immunother 2009;58:823-30.
22. Hoos A, Eggermont AM, Janetzki S et al. Improved endpoints for cancer immunotherapy trials. J Natl Cancer Inst 2010;102:1388-97.
23. Shi SB, Tang XY, Tian J, Chang CX, Li P, Qi JL. Efficacy of erlotinib plus dendritic cells and cytokine-induced killer cells in maintenance therapy of advanced non-small cell lung cancer. J Immunother 2014;37:250-5.
24. Zhong R, Han B, Zhong H. A prospective study of the efficacy of a combination of autologous dendritic cells, cytokine-induced killer cells, and chemotherapy in advanced non-small cell lung cancer patients. Tumour Biol 2014;35:987-94.
25. Yuanying Y, Lizhi N, Feng M et al. Therapeutic outcomes of combining cryotherapy, chemotherapy and DC-CIK immunotherapy in the treatment of metastatic non-small cell lung cancer. Cryobiology 2013;67:235-40.