CrossMark

ORIGINAL ARTICLE

# Clinical effects of autologous dendritic cells combined with cytokine-induced killer cells followed by chemotherapy in treating patients with advanced colorectal cancer: a prospective study

Tao Lin[1] · Chun Song[1] · Dong-yu Chuo[1] · Hao Zhang[1] · Jian Zhao[1]

**Abstract** The objective of this study was to evaluate the effects of dendritic cell and cytokine-induced killer (DC-CIK) cell-based immunotherapy combined with chemotherapy on the treatment of patients with advanced colorectal cancer. We prospectively included patients with advanced colorectal cancer and assessed the efficacy of DC-CIK cell-based immunotherapy combined with chemotherapy compared to treatment with chemotherapy alone. T cell subtypes, progression-free survival (PFS), overall survival (OS), and adverse events were evaluated in each group. In total, 134 patients were included in the DC-CIK group and 121 patients were included in the control group. No significant differences were observed in the percentages of $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, and NK cells after DC-CIK cell-based immunotherapy compared to before chemotherapy in the DC-CIK group. The median PFS and OS in the DC-CIK treatment group were 8.8 months (95 % CI 8.4–9.1) and 14.7 months (95 % CI 13.9–15.5), respectively, which were significantly improved compared to the PFS and OS in the control group. The frequencies of grade III and IV leukopenia (8.2 vs. 19.0 %, $P=0.011$), grade III and IV anemia (3.0 vs. 9.1 %, $P=0.039$), and grade III and IV thrombocytopenia (3.7 vs. 10.7 %, $P=0.029$) were significantly lower in the DC-CIK group compared to the control group. DC-CIK cell-based immunotherapy could induce an immune response against colorectal cancer and prolong PFS and OS. DC-CIK cell-based immunotherapy combined with chemotherapy had a significant benefit in terms of survival in patients with colorectal cancer compared to chemotherapy alone.

**Keywords** Immunotherapy · Dendritic cells · Cytokine-induced killer cell · Colorectal cancer

## Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors worldwide, with a greater than 50 % fatality rate [1]. Generally, the standard treatment modalities for CRC are surgery, radiotherapy, and chemotherapy, which have proven clinical benefits for patients [2–4]. Patients with early-stage CRC are usually offered resection followed by adjuvant chemotherapy and radiotherapy, and their 5-year survival rate can be up to 80 % [4]. Nevertheless, most patients with early-stage CRC are asymptomatic and the disease has often progressed to the advanced stage by the time it is clinically diagnosed. In addition, certain populations of patients with early-stage CRC will eventually develop advanced-stage disease with a 5-year survival rate of less than 5 % [5]. The first-line treatment for advanced CRC is chemotherapy. Chemotherapy has several shortcomings, including severe treatment-related toxicity and poor general health of patients, leading to treatment discontinuation and resulting in an inability to completely eradicate the tumor in patients with advanced CRC [6].

Because patients are in an immunosuppressed state when they undergo surgery, radiotherapy, and chemotherapy, immunotherapy can be used to recover anticancer immunity and to help build a specific and effective immune response to kill tumor cells. Dendritic cell and

✉ Chun Song
songchunln@163.com

[1] Department of Colorectal Surgery, Liaoning Cancer Hospital & Institute, NO. 44 Xiaoheyan Road, Dadong District, Shenyang 110042, Liaoning Province, China

 Springer

cytokine-induced killer (DC-CIK) cell-based immunotherapy is one of the most effective tools to kill residual cancer cells and has good tolerance and excellent compliance [7–9]. However, reports regarding the effects of DC-CIK cell-based immunotherapy combined with chemotherapy on treating patients with advanced CRC are scarce.

From January 2011 to November 2014, we conducted a prospective study to evaluate the effects of DC-CIK cell-based immunotherapy followed by chemotherapy on the treatment of advanced CRC.

## Patients and methods

### Patients

In total, 255 patients with advanced CRC who were diagnosed and treated at the Liaoning Cancer Center and Institute between January 2011 and December 2014 were included. These patients were classified randomly into two groups: the DC-CIK group, which included patients who received chemotherapy and autologous DC-CIK cell-based immunotherapy ($n=134$), and the control group, which included patients who received only chemotherapy ($n=121$).

All patient diagnoses were confirmed histologically or cytologically; CT scanning was also used when necessary. The tumor node metastases (TNM) staging system of the American Joint Committee on Cancer/Union for International Cancer Control was used to confirm CRC stage or differentiation. The inclusion criteria were as follows: (1) histologically or cytologically diagnosed advanced CRC, (2) unresectable CRC at the first diagnosis or relapsed/metastatic CRC after surgery, (3) expected survival of more than 3 months, (4) a Karnofsky performance status score higher than 60 and adequate renal function and peripheral lymphocyte and monocyte numbers to receive DC-CIK cell-based therapy, and (5) no other previous tumor history.

During the first year following initial treatment in this study, all the patients were followed up every month; in the subsequent years, all the patients were followed up every 2 months. The end point was December 31, 2014, or the time of death. Progression-free survival (PFS) was defined as the time from the date of surgery to the first progression or the date of last contact. Overall survival (OS) was defined as the time from the date of surgery to either the date of death or the date of last follow-up.

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the ethical committee of the Liaoning Cancer Hospital and Institute, and informed consent was obtained from all participants included in the study.

### Treatment

All the patients in the two groups were offered 6 cycles of multidrug adjuvant chemotherapy (5-FU, FOLFOX/XELOX) [10–12]. Then, the patients in the DC-CIK group received a total of five autologous DC-CIK cell treatments at 1-month intervals. Venous blood samples (5 ml) from each patient were obtained to analyze CIK phenotypes before and after DC-CIK cell transfusion. The patients in the control group did not receive DC-CIK cell-based immunotherapy after 6 cycles of chemotherapy.

### DC-CIK cell-based immunotherapy

The schedule of autologous DC-CIK cell-based immunotherapy was performed based on the "Treatment with Autologous Immune Cells" policy of the Ministry of Health of China as described previously [13, 14]. Initially, using the Fresenius KABI System (Germany), peripheral blood mononuclear cells (PBMCs) were collected and cultured, and then monocytes (adherent cells) and lymphocytes (adherent cells) were separated.

The autologous DCs and CIK cells were prepared as follows [13, 15, 16]. Cancer lysates were prepared to pulse DCs. A single-cell suspension of SW480 colon tumor cells was dissociated by ultrasound and centrifugation for 30 min, and the cellular supernatants were collected as the tumor lysate. DCs were obtained by culturing the adherent cells and stimulating them with tumor lysate and interleukin (IL)-4 for 7 days. We obtained SW480 CIK cells by culturing the nonadherent cells for 10 days.

We emphasized quality control of both the DCs and CIK cells. The immune phenotypes, such as $CD3^+CD8^+$ for DCs and $CD3^+$ for CIK cells, were evaluated using flow cytometry [17]. The fungus, bacteria, and endotoxin levels in cultured DC and CIK samples complied strictly with the release criteria for infusion [18–20]. In total, $1 \times 10^7$ DCs were drawn for intradermal vaccination or were mixed with 100 ml normal saline for intravenous injection, and $1 \times 10^9$ CIK cells were mixed with 100 ml normal saline for intravenous infusion.

### Statistical analysis

Differences in clinical characteristics between the two groups were assessed using the $\chi^2$ test. The diversities in

**Table 1** Clinical characteristics of the patients in the two groups

| Characteristics | DC-CIK (N=134) | Control (N=121) | Statistics and P values |
|---|---|---|---|
| Sex | | | |
|     Male | 76 | 64 | $\chi^2=0.375$, $P=0.540$ |
|     Female | 58 | 57 | |
| Age | | | |
|     <60 | 79 | 68 | $\chi^2=0.198$, $P=0.656$ |
|     ≥60 | 55 | 53 | |
| Primary lesion | | | |
|     Colon | 75 | 68 | $\chi^2=0.001$, $P=0.971$ |
|     Rectum | 59 | 53 | |
| Tumor size (cm) | | | |
|     <4 | 71 | 57 | $\chi^2=0.879$, $P=0.349$ |
|     ≥4 | 63 | 64 | |
| Histologic differentiation | | | |
|     Poorly differentiated | 69 | 53 | $\chi^2=1.51$, $P=0.220$ |
|     Moderate differentiation | 65 | 68 | |
| Histologic type | | | |
|     Adenocarcinoma | 120 | 110 | $\chi^2=0.132$, $P=0.716$ |
|     Other | 14 | 11 | |

T cell subtype distributions were expressed as the mean± SE and were evaluated using the Student's $t$ test. The OS and PFS curves were evaluated by the Kaplan-Meier method. All analyses were conducted using SPSS software (version 18.0) with two-tailed $P$ values. $P=0.05$ indicated statistical significance.

## Results

**Characteristics of patients** The clinical characteristics of the patients are summarized in Table 1. No significant differences regarding sex, age, primary lesion, tumor size, histological differentiation, or histological type were observed between the DC-CIK and control groups.

**Phenotypic analysis of DC-CIK cells** The T lymphocyte subsets in the peripheral blood samples of the patients in the two groups were analyzed before and after treatment. No significant differences in the percentages of CD3$^+$, CD3$^+$CD4$^+$, CD3$^+$CD8$^+$, and NK cell subsets were observed after DC-CIK therapy compared to before chemotherapy in the DC-CIK group, while significant decreases in all the cell subsets were observed in the control group. In addition, all these cell subsets were significantly higher in the DC-CIK-treated patients than in those treated with chemotherapy alone (Table 2). Furthermore, the expression of IFN-$\gamma$, IL-2, and TNF-$\alpha$ in CD4$^+$ T cells was significantly higher after DC-CIK cell-based immunotherapy than after treatment with chemotherapy alone (Table 3).

**PFS and OS** During the follow-up period, the median PFS and OS in the DC-CIK group were 8.8 months (95 % CI

**Table 2** Diversities in T cell subtype distribution in the two groups (mean±SE, %)

| Group | CD3$^+$ | CD3$^+$CD4$^+$ | CD3$^+$CD8$^+$ | NK | NKT | Treg |
|---|---|---|---|---|---|---|
| DC-CIK | | | | | | |
|   Before chemotherapy | 71.4±14.7 | 36.7±8.2 | 27.4±7.1 | 12.4±4.4 | 4.8±1.0 | 7.9±1.3 |
|   After DC-CIK therapy | 68.7±13.9 | 35.0±6.6 | 25.8±6.5 | 11.1±6.6 | 3.1±1.7* | 6.5±1.5* |
| Control | | | | | | |
|   Before chemotherapy | 72.5±13.5 | 38.6±8.6 | 29.1±7.8 | 14.1±6.6 | 4.5±2.5 | 8.0±2.5 |
|   After 6 cycles of chemotherapy | 44.7±10.3*·** | 24.4±5.8*·** | 18.5±9.4*·** | 5.6±4.9*·** | 2.5±2.4*·** | 6.0±3.9*·** |

*$P<0.05$, before versus after treatment in each group; **$P<0.05$, posttreatment comparisons between the two groups

**Table 3** Diversities in intracellular cytokines in CD4$^+$ T cells in the two groups after treatment (mean±SE, %)

| Group | IFN-γ | IL-2 | TNF-α |
|---|---|---|---|
| DC-CIK | | | |
| Before chemotherapy | 8.3±2.3 | 10.7±4.0 | 8.3±3.4 |
| After DC-CIK therapy | 7.7±3.4 | 10.0±3.0 | 7.6±2.5 |
| Control | | | |
| Before chemotherapy | 7.8±3.5 | 11.5±2.7 | 7.9±3.0 |
| After 6 cycles chemotherapy | 4.5±2.2*·** | 5.2±1.6*·** | 3.9±1.5*·** |

*$P<0.05$, before versus after treatment in each group; **$P<0.05$, post-treatment comparisons between the two groups

8.4–9.1) and 14.7 months (95 % CI 13.9–15.5), respectively, which were significantly improved compared to the control group (PFS 5.8 months, 95 % CI 5.4–5.9; OS 10.8 months, 95 % CI 10.3–11.3). The PFS and OS curves for the DC-CIK and control groups are shown in Figs. 1 and 2, respectively.

**Adverse events** Severe treatment-induced hematological toxicities included leukopenia, anemia, thrombocytopenia, nausea, vomiting, and abnormal liver function. The frequencies of grade III and IV leukopenia (8.2 vs. 19.0 %, $P=0.011$), grade III and IV anemia (3.0 vs. 9.1 %, $P=0.039$), and grade III and IV thrombocytopenia (3.7 vs. 10.7 %, $P=0.029$) were

significantly lower in the DC-CIK group compared to the control group (Table 4).

## Discussion

Although various therapeutics for CRC, such as chemotherapy, radiotherapy, and hyperthermia, have been developed in recent years, the prognosis of advanced CRC remains poor [6, 7, 21]. Therefore, exploring multidisciplinary approaches and multiple treatment options may be necessary. Cytokine immunotherapy has become a standard treatment for cancer and has exhibited encouraging progress in preventing tumor progression and recurrence after surgery [8, 22, 23]. Immunotherapy can stimulate the natural immunity of patients to recognize and induce tumor cell death with fewer adverse effects [4, 24, 25]. CIK cells are cytotoxic lymphocytes with enhanced cytotoxicity and high proliferation generated from peripheral lymphocytes [26]. As previous studies have shown, the interactions between DCs and CIK cells can elicit changes in surface molecule expression in both populations and can lead to improved cytotoxic activity [7, 8, 15, 27]. Therefore, DCs combined with CIK cells may have clinical benefits for patients with cancer. However, studies evaluating the effects of combining standard chemotherapy with DC-CIK
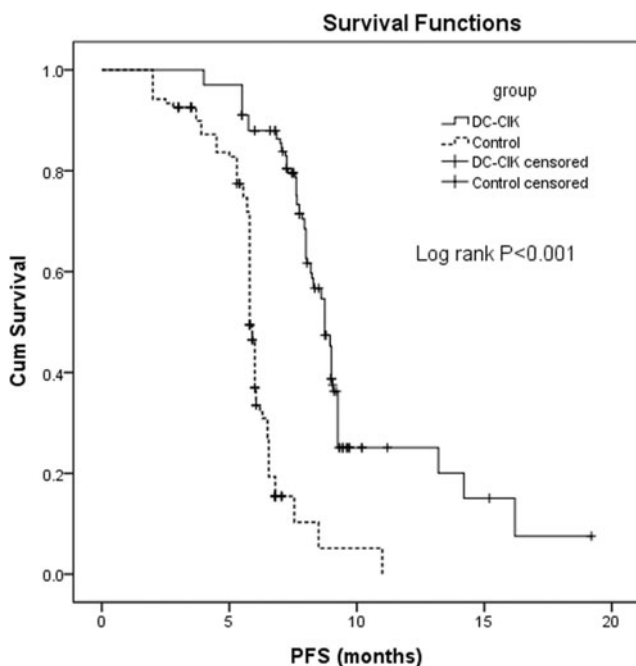


**Fig. 1** PFS after treatment in patients who received chemotherapy and DC-CIK cell-based immunotherapy and in patients who received chemotherapy alone
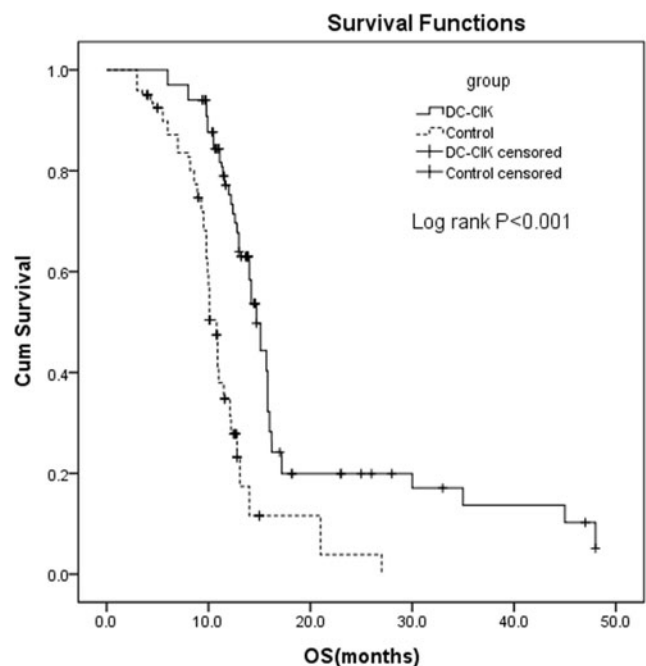


**Fig. 2** OS after treatment in patients who received chemotherapy and DC-CIK cell-based immunotherapy and in patients who received chemotherapy alone

**Table 4** Adverse events reported in the two groups

| Adverse events | DC-CIK (N=134) | | | | | Control (N=121) | | | | | Statistics and P values[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | I | II | III | IV | 0 | I | II | III | IV | |
| Leukopenia | 9 | 23 | 15 | 7 | 4 | 16 | 27 | 31 | 17 | 6 | $\chi^2$=6.417, P=0.011 |
| Anemia | 34 | 16 | 18 | 2 | 2 | 34 | 44 | 28 | 6 | 5 | $\chi^2$=4.273, P=0.039 |
| Thrombocytopenia | 20 | 15 | 18 | 3 | 2 | 22 | 29 | 37 | 11 | 2 | $\chi^2$=4.776, P=0.029 |
| Nausea, vomiting | 17 | 24 | 33 | 3 | 1 | 17 | 39 | 46 | 7 | 2 | $\chi^2$=2.606, P=0.106 |
| Abnormal liver function | 24 | 11 | 17 | 2 | 1 | 30 | 17 | 31 | 4 | 3 | $\chi^2$=2.122, P=0.145 |

[a] Proportion of grade III and IV events in the DC-CIK group compared to the control group

immunotherapy in patients with advanced CRC are scarce [13, 15]. This study presents clinical evidence supporting the hypothesis that the combination of DC-CIK immunotherapy with chemotherapy could benefit patients with advanced CRC.

No significant differences were observed in the T lymphocytes subsets in the peripheral blood samples of patients after DC-CIK therapy compared to before chemotherapy in the DC-CIK group, which may be attributed to the DC-CIK therapy. Several studies have shown that CIK cells can induce the apoptosis of and exhibit strong cytotoxicity toward drug-resistant tumor cells, and these CIK cells can produce IL-2, IFN-$\gamma$, and other antitumor cytokines [28–30]. These chemokines may function with IFN-$\gamma$ to potentially tilt the immune response in the direction of helper T (TH) 1 cells [27].

Studies have shown that DC-CIK or CIK cell-based therapy benefits patients with cancer [13, 21, 31, 32]. Moon Jae Chung reported that the PFS of patients with advanced pancreatic cancer who were treated with ex vivo-expanded CIK cells was 26 weeks, which was relatively longer than that for patients treated with only chemotherapy [33]. Zhang et al. conducted a retrospective study to evaluate the effects of CIK treatment in 60 patients with colorectal cancer and showed that the median PFS and median OS in the CIK group were 25.8 and 41.3 months, respectively, which were significantly longer compared to our results (median PFS, 8.8 months; OS, 14.7 months) [21]. This discrepancy could be explained by the facts that the patients in our study had unresectable CRC or relapsed/metastatic CRC after surgery and that most of our patients had a poor prognosis. Nevertheless, both the PFS and OS in the DC-CIK treatment group were significantly longer than those in the control group. Niu et al. retrospectively compared the combination of DC-CIK cell-based immunotherapy and chemotherapy with chemotherapy alone and concluded that the combination of DC-CIK cell-based

immunotherapy and chemotherapy could induce an immune response against colorectal cancer and prolong OS [13]. Another study of patients with late-stage non-small cell lung cancer showed that DC-CIK cell-based immunotherapy synergized with chemotherapy and prolonged patient survival [14]. All these studies indicate that DC-CIK cell-based immunotherapy may synergize with chemotherapy to elicit potent systemic antitumor activity. Although DC-CIK or CIK cell-based therapy can be of clinical benefit to patients with advanced CRC, the differences of clinical benefit between DC-CIK cell-based immunotherapy and CIK cell-based immunotherapy should be further studied to fully understand their functions.

The combination of DC-CIK cell-based immunotherapy with conventional chemotherapy has proven to be safe and feasible [17, 20]. In this study, the adverse events that are usually observed with conventional chemotherapy, namely, grade III and IV leukopenia, anemia, and thrombocytopenia, were less likely to occur in the DC-CIK group. Therefore, the combined therapy exhibited good tolerability and safety.

In conclusion, DC and CIK cell-based immunotherapy could induce an immune response against colorectal cancer and prolong PFS and OS. Furthermore, this therapy proved to be safe and had a significant benefit in patients with CRC in terms of survival compared to chemotherapy alone.

# References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
2. Hontscha C, Borck Y, Zhou H, Messmer D, Schmidt-Wolf IGH. Clinical trials on CIK cells: first report of the international registry on CIK cells (IRCC). J Cancer Res Clin Oncol. 2011;137:305–10.
3. Stroncek D, Berlyne D, Fox B, Gee A, Heimfeld S, Lindblad R, et al. Developments in clinical cell therapy. Cytotherapy. 2010;12:425–8.
4. Okada N. Cell delivery system: a novel strategy to improve the efficacy of cancer immunotherapy by manipulation of immune cell trafficking and biodistribution. Biol Pharm Bull. 2005;28:1543–50.
5. Zoll B, Lefterova P, Csipai M, Finke S, Trojaneck B, Ebert O, et al. Generation of cytokine-induced killer cells using exogenous interleukin-2, -7 or -12. Cancer Immunol Immunother. 1998;47:221–6.
6. Chau I, Cunningham D. Treatment in advanced colorectal cancer: what, when and how? Br J Cancer. 2009;100:1704–19.
7. Shapira S, Lisiansky V, Arber N, Kraus S. Targeted immunotherapy for colorectal cancer: monoclonal antibodies and immunotoxins. Expert Opin Investig Drugs. 2010;19:S67–77.
8. Dougan M, Dranoff G. Immune therapy for cancer. Annu Rev Immunol. 2009;27:83–117.
9. Sangiolo D, Martinuzzi E, Todorovic M, Vitaggio K, Vallario A, Jordaney N, et al. Alloreactivity and anti-tumor activity segregate within two distinct subsets of cytokine-induced killer (CIK) cells: Implications for their infusion across major HLA barriers. Int Immunol. 2008;20:841–8.
10. Ling W, Fan J, Ma Y, Ma Y, Wang H. Capecitabine-based chemotherapy for metastatic colorectal cancer. J Cancer Res Clin Oncol. 2011;137:927–38.
11. Sanoff HK, Carpenter WR, Freburger J, Li L, Chen K, Zullig LL, et al. Comparison of adverse events during 5-fluorouracil versus 5-fluorouracil/oxaliplatin adjuvant chemotherapy for stage III colon cancer a population-based analysis. Cancer. 2012;118:4309–20.
12. Zhu Y, Zhang H, Li Y, Bai J, Liu L, Liu Y, et al. Efficacy of postoperative adjuvant transfusion of cytokine-induced killer cells combined with chemotherapy in patients with colorectal cancer. Cancer Immunol Immunother. 2013;62:1629–35.
13. Niu JX, Ren YJ, Zhang TY, Yang XJ, Zhu W, Zhu H, et al. Retrospective comparative study of the effects of dendritic cell vaccine and cytokine-induced killer cell immunotherapy with that of chemotherapy alone and in combination for colorectal cancer. Biomed Res Int. 2014;2014:214727.
14. Zhong RB, Teng JJ, Han BH, Zhong H. Dendritic cells combining with cytokine-induced killer cells synergize chemotherapy in patients with late-stage non-small cell lung cancer. Cancer Immunol Immunother. 2011;60:1497–502.
15. Sabado RL, Bhardwaj N. Directing dendritic cell immunotherapy towards successful cancer treatment. Immunotherapy. 2010;2:37–56.
16. Janikashvili N, Larmonier N, Katsanis E. Personalized dendritic cell-based tumor immunotherapy. Immunotherapy. 2010;2:57–68.
17. Li X-D, Xu B, Wu J, Ji M, Xu B-H, Jiang J-T, et al. Review of Chinese clinical trials on CIK cell treatment for malignancies. Clin Transl Oncol. 2012;14:102–8.
18. Schmidt-Wolf IGH, Finke S, Trojaneck B, Denkena A, Lefterova P, Schwella N, et al. Phase I clinical study applying autologous immunological effector cells transfected with the interleukin-2 gene in patients with metastatic renal cancer, colorectal cancer and lymphoma. Br J Cancer. 1999;81:1009–16.
19. Cui Y, Yang X, Zhu W, Li J, Wu X, Pang Y. Immune response, clinical outcome and safety of dendritic cell vaccine in combination with cytokine-induced killer cell therapy in cancer patients. Oncol Lett. 2013;6:537–41.
20. Liu Y, Zhang W, Zhang B, Yin X, Pang Y. Dc vaccine therapy combined concurrently with oral capecitabine in metastatic colorectal cancer patients. Hepatogastroenterology. 2013;60:23–7.
21. Zhang JY, Zhu LJ, Zhang Q, He X, Yin YM, Gu YH, et al. Effects of cytokine-induced killer cell treatment in colorectal cancer patients: a retrospective study. Biomed Pharmacother. 2014;68:715–20.
22. Zhong H, Han B, Tourkova IL, Lokshin A, Rosenbloom A, Shurin MR, et al. Low-dose paclitaxel prior to intratumoral dendritic cell vaccine modulates intratumoral cytokine network and lung cancer growth. Clin Cancer Res. 2007;13:5455–62.
23. Hui KM. Cik cells - current status, clinical perspectives and future prospects - the good news. Expert Opin Biol Ther. 2012;12:659–61.
24. Lu PH, Negrin RS. A novel population of expanded human cd3+cd56+ cells derived from t-cells with potent in-vivo antitumor-activity in mice with severe combined immunodeficiency. J Immunol. 1994;153:1687–96.
25. Margolin KA, Negrin RS, Wong KK, Chatterjee S, Wright C, Forman SJ. Cellular immunotherapy and autologous transplantation for hematologic malignancy. Immunol Rev. 1997;157:231–40.
26. Hoos A, Eggermont AMM, Janetzki S, Hodi FS, Ibrahim R, Anderson A, et al. Improved endpoints for cancer immunotherapy trials. J Natl Cancer Inst. 2010;102:1388–97.
27. Marten A, Ziske C, Schottker B, Renoth S, Weineck S, Buttgereit P, et al. Interactions between dendritic cells and cytokine-induced killer cells lead to an activation of both populations. J Immunother. 2001;24:502–10.
28. Ma Y, Zhang Z, Tang L, Xu YC, Xie ZM, Gu XF, et al. Cytokine-induced killer cells in the treatment of patients with solid carcinomas: a systematic review and pooled analysis. Cytotherapy. 2012;14:483–93.
29. Lu W, Li Y-H, He X-F, Chen Y, Zeng Q-L, Qiu Y-R. Effect of dosage of anticancer agents during transcatheter arterial chemoembolization on t cell subsets in patients with hepatocellular carcinoma. Di Yi Jun Yi Da Xue Xue Bao. 2002;22:524–6.
30. Zhang Y-S, Yuan F-J, Jia G-F, Zhang J-F, Hu L-Y, Huang L, et al. CIK cells from patients with HCC possess strong cytotoxicity to multidrug-resistant cell line Bel-7402/R. World J Gastroenterol. 2005;11:3339–45.
31. Zhang G, Zhao H, Wu J, Li J, Xiang Y, Wang G, et al. Adoptive immunotherapy for non-small cell lung cancer by NK and cytotoxic T lymphocytes mixed effector cells: retrospective clinical observation. Int Immunopharmacol. 2014;21:396–405.
32. Introna M, Golay J, Rambaldi A. Cytokine induced killer (CIK) cells for the treatment of haematological neoplasms. Immunol Lett. 2013;155:27–30.
33. Chung MJ, Park JY, Bang S, Park SW, Song SY. Phase II clinical trial of ex vivo-expanded cytokine-induced killer cells therapy in advanced pancreatic cancer. Cancer Immunol Immunother. 2014;63:939–46.