ORIGINAL RESEARCH

Chemotherapy combined with dendritic cell vaccine and cytokine-induced killer cells in the treatment of colorectal carcinoma: a meta-analysis

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Aim: To investigate the efficacy and safety of dendritic cell (DC) vaccine combined with cytokine-induced killer (CIK) cell therapy in colorectal carcinoma (CRC).

Patients and methods: PubMed, Embase, and Cochrane Library databases were searched systematically for clinical trials of DC vaccine and CIK cell therapy combined with chemotherapy for CRC. The primary and secondary endpoints were overall survival (OS) and disease-free survival (DFS), respectively. Pooled risk ratios were used to assess the treatment efficacy. Both random and fixed effects models were used for statistical analysis. The study population consisted of 871 CRC patients enrolled in four trials.

Results: OS and DFS were significantly improved in patients who received chemotherapy combined with DC vaccine and CIK cells, and no severe adverse events were shown.

Conclusions: The study demonstrated that the addition of DC vaccine and CIK cell therapy to chemotherapy is feasible and effective in patients with CRC.

Keywords: adoptive cellular therapy, immunotherapy, dendritic cell vaccine, cytokine-induced killer cell, overall survival, disease-free survival, colorectal carcinoma

Introduction

Colorectal carcinoma (CRC) is now the third most common cancer, accounting for 9% of the new cancer cases in men and 8% of the new cancer cases in women in 2017, as estimated by the American Cancer Society.[36] More importantly, about 25% of patients with CRC have distant metastasis upon diagnosis, with liver metastasis in most cases. Only 20% of liver metastasis cases are eligible for radical surgery.[34] Furthermore, traditional therapies, such as chemotherapy and radiotherapy, usually fail to eradicate colorectal tumors completely, and their clinical applications are limited by accompanying adverse events.[11,35] Thus, novel treatment and early diagnosis of CRC are pressing needs, and immunotherapy may serve as an alternative due to the encouraging results.[2,14,30]

Recently, how to better fight cancer by restoring and enhancing immune function has attracted great interest. Clinical evidence demonstrates that immunotherapy may be an effective and safe supplementary approach to cancer treatment.[7,9,15,22] Some studies reported that immunotherapy could improve the efficacy of chemotherapy and radiotherapy for CRC patients.[6,10,23] Many immunotherapy investigations are ongoing, including those of cancer vaccines, adoptive cellular therapy, and immunomodulatory antibodies such as ipilimumab and pembrolizumab, and obtaining sufficient numbers of immune effectors to improve the efficiency of recognizing tumor targets is one of the most notable problems.

Dendritic cells (DCs) are critical for the robust presentation of immunogenic peptides and activation of T cells.[38] DCs can be generated from human peripheral blood mononuclear cells (PBMCs) ex vivo by stimulating with interleukin (IL)–4, granulocyte macrophage colony-stimulating factor (GM-CSF), and tumor-associated antigen. Then, mature DCs can be transferred back into patients as a cancer vaccine to elicit an antigen-specific immune reaction.[27,29,33] Clinical studies demonstrated that DC vaccines could elicit different clinical benefits in metastatic melanoma, lymphoma, non-small-cell lung cancer, and CRC.[6,41,43] Sipuleucel-T (APC8015) is one of the DC vaccines, proliferated from PBMCs by culturing with a prostatic acid phosphatase (PAP), a fusion protein of prostate cancer antigen and GM-CSF, and it could prolong overall survival in prostate cancer patients;[1] thus, it was approved by the FDA for the treatment of metastatic prostate cancers.

Cytokine-induced killer (CIK) cells are immune effector cells that are easy to proliferate from PBMCs through stimulating with interferon (IFN)-γ, CD3 monoclonal antibody, and IL-2. These cells show a high proliferation rate of the $CD3^+$ $CD56^+$ phenotype, take advantage of the body's natural ability to eliminate tumor cells by stimulating and restoring the immune system to recognize and kill tumor cells, exhibit robust antitumor activity, and have no major histocompatibility complex restrictions;[11,18,21] thus, they are frequently used in cellular immunotherapy for a variety of malignancies.[46,51] As reported by Hontscha,[11] CIK treatment could significantly improve disease-free survival (DFS) rates and prevent recurrence for cancer patients, compared with the control group.

DCs have been proved to play an important role in CIK activation, proliferation, phenotype expression, and cytokine secretion by direct contact and secreted IL-12, IFN-γ, and TNF-a, which enhance antitumor effects.[13,22,32,47] After co-culture with DCs, $CD3^+$ $CD56^+$ cells, which are the main effector cells enhancing CIK cytotoxicity, were increased, whereas $CD4^+$ $CD25^+$ regulatory T cells, which inhibit CIK antitumor activity, were decreased.[32,47] In addition, CIK cells promote DC maturation and expression of co-stimulatory molecules, such as CD40, CD80, and CD86,[24,47] and the combination of DC and CIK provides a remarkably increased cytotoxic activity.[46] It has also been found that the combination of DC and CIK is more effective than CIK treatment.[53]

Combination therapy with CIK cells and DC vaccine has been successfully applied to treat cancers, such as glioblastoma, non-small-cell lung cancer, and advanced renal cell carcinoma, and it has been demonstrated that this therapy can enhance host cellular immune responses, prolong survival time, and improve quality of life.[19,40,45,49] Mao et al[20] reported

that DC vaccine and CIK cell combined with chemotherapy are able to improve the disease control rate (DCR) and living quality of patients, with no severe side effects in patients with metastatic breast cancer. However, recent clinical trials on the DC vaccine and CIK cells in CRC patients are still based on small sample size and a lack of high-quality data from multicenter studies. So, we conducted this meta-analysis with the aim of investigating the efficacy and safety of combination therapy with DC vaccine and CIK cell for CRC, which will help future clinical trials.

Methods

Literature search strategy
PubMed, Embase, and Cochrane Library databases were searched with no date restrictions for "colorectal cancer," "cytokine-induced killer cells," and "dendritic cells." All of the articles were subjected to strict reviews, including full text, authors, and research institutions, to eliminate duplicate versions.

Selection criteria
The articles we identified in this search were required to meet the following inclusion criteria for the present meta-analysis: (1) the report was of a human trial published in English; (2) the patients had histologically or cytologically proven CRC diagnosis; (3) the combination therapy group received both chemotherapy and more than one cycle of DC vaccine and CIK cell therapy, whereas the control group received chemotherapy alone; and (4) the primary outcome measure in the study was overall survival (OS). Case studies were excluded.

Data extraction
Data extraction was conducted by two investigators using a standardized approach. Divergences in what to collect were adjudicated by a third investigator after reading the original publications. We collected information from the publication, including the authors' name, sample size per arm, tumor stage, and the percentages of OS and DFS. Randomized controlled trials were assessed using the Jadad et al[12] format, and the quality of the retrospective studies was assessed using the Newcastle-Ottawa Scale.[37]

Efficacy assessments
We evaluated both OS and DFS of the four studies. OS was defined as the time from the start of a clinical trial to death due to any cause, and DFS was defined as the time from surgery to tumor recurrence or death by authors of included

studies. We used Engauge Digitizer to extract data from the survival curves of the included studies,[55] and then used the Excel table provided by Tierney et al[42] for data reconstruction.

Statistical analysis

Statistical analysis was performed using the Review Manager software program (version 5.3; Cochrane, London, UK). *P*-values less than 0.05 were considered as significant. Risk ratios (RRs) and their 95% confidence intervals (CIs) were used for calculations. Heterogeneity analysis of the included trials was performed before combining data using Cochran's chi-squared test (Q test), with significance set at *P*-values less than 0.10. Because heterogeneity in the four studies may be difficult to detect, we evaluated both random effects and fixed effects.

Results

Selection of the trials

The initial literature search found 153 related articles, but 143 publications were excluded because 97 were reviews, 15 were case reports, and 31 were not CRC. After referring to full texts, six publications that failed to meet the inclusion criteria were excluded because three did not involve CIKs, two did not involve DCs, and one did not involve chemotherapy combined with DCs and CIK cells. Ultimately, there were only four clinical trials, which involved a total of 871 patients, that matched our inclusion criteria.[8,17,25,54] The selection procedure is shown in Figure 1.

Characteristics of the eligible trials

All four trials were fully published and consisted of two randomized studies and two retrospective analyses. The

researchers in the studies prepared DC vaccines by culturing PBMCs of CRC patients in the presence of tumor lysates, GM-CSF, tumor necrosis factor, and IL-4. In addition, investigators used CD3 monoclonal antibody, IFN-γ, and IL-2 in the CIK cell cultures in all of these trials. The mean number of DCs transfused into the patients in these studies was 1×10^7 per course, whereas that of CIK cells was more than 1×10^9 per course. The information about the publication, including the authors' name, sample size per arm, tumor stage, and the percentages of OS and DFS, were also collected (Table 1).

Six-month OS

We found that DC-CIK cell therapy significantly improved six-month OS, whether using fixed or random effects models for statistical analysis (fixed effects model: RR=1.11 [95%
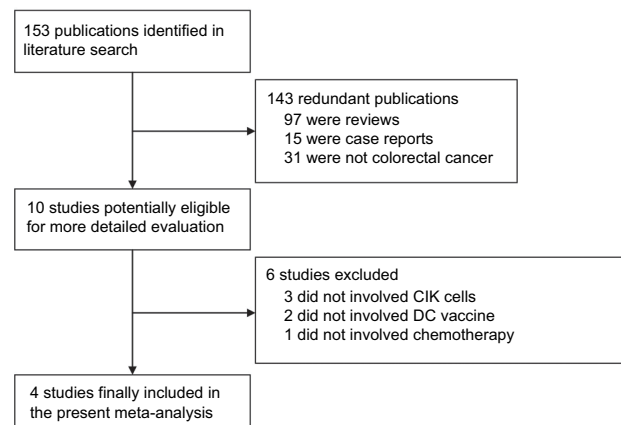

Figure 1 Flow diagram of the article search, screening, and study inclusion process.
Abbreviations: CIK, cytokine-induced killer; DC, dendritic cell.

Table 1 Clinical information on the patients in the four eligible trials

Study	Tumor stage	All patients (male patients)	CIK regimen	DC regimen	CIK cell culture conditions	DC culture conditions
Gao et al[8]	I–IV	26 (U)	$5.9\pm2.2\ 10^9$	$1.9\pm7.9\ 10^7$	IL-2, IFN-γ, CD3	Tumor lysate IL-4, GM-CSF
Lin et al[17]	IV	255 (140)	$1.0\ 10^9$	$1.0\ 10^7$	IL-2, IFN-γ, CD3	Tumor lysate IL-4, GM-CSF TNF
Niu et al[25]	I–IV	239 (113)	$1.0\ 10^9$	$1.0\ 10^7$	IL-2, IFN-γ, CD3	Tumor lysate IL-4, GM-CSF TNF
Zhu et al[54]	IV	351 (229)	$1.0\ 10^9$	$1.0\ 10^7$	IL-2, IFN-γ, CD3	Tumor lysate IL-4, GM-CSF TNF
Study	0.5-year OS (%) of DC-CIK/ chemo (chemo)	1-year OS (%) of DC-CIK/ chemo (chemo)	1.5-year OS (%) of DC-CIK/ chemo (chemo)	2-year OS (%) of DC-CIK/ chemo (chemo)	0.5-year DFS (%) of DC-CIK/chemo (chemo)	1-year DFS (%) of DC-CIK/chemo (chemo)
Gao et al[8]	100 (84.6)	100 (76.9)	100 (53.8)	92.3 (41.2)	100 (76.9)	100 (69.2)
Lin et al[17]	100 (90.1)	74.6 (34.7)	24.6 (9.1)	22.4 (7.4)	—	—
Niu et al[25]	76.5 (45.5)	47.1 (18.2)	—	—	52.7 (34.6)	21.6 (9.2)
Zhu et al[54]	90 (83.7)	81 (69.7)	72 (57.8)	—	—	—

Abbreviations: CIK, cytokine-induced killer; DC, dendritic cell; U, unknown; GM-CSF, granulocyte macrophage colony-stimulating factor; TNF, tumor necrosis factor; OS, overall survival; DC-CIK/chemo, DC vaccine and CIK cell immunotherapy combined with chemotherapy; Chemo, chemotherapy alone; DFS, disease-free survival.

CI=1.05–1.17], *P*=0.0001; random effects model: RR=1.10 [95% CI=1.05–1.16], *P*<0.001). The 6-month OS rate was 94.7% (250/264) in the patients who received the combination therapy and 84.6% (335/396) in those who received chemotherapy only. We did not detect statistically significant heterogeneity in the four studies (χ^2=2.06, df=3, *P*=0.56, I^2=0%) (Figures 2 and 3).

One-year OS

The 1-year OS rates were 58.1% (230/396) and 76.5% (202/264) in the control and combination therapy groups, respectively. The estimated pooled RR for the four trials improved significantly in 1-year OS for patients in the

combination group (fixed effects model: RR=1.46 [95% CI=1.30–1.64], *P*<0.0001; random effects model: RR=1.52 [95% CI=1.01–2.27], *P*=0.040). However, we found statistically significant heterogeneity in the four trials (χ^2=21.68, df=3, *P*<0.001, I^2=86%) (Figures 2 and 3).

One and a half-year OS

Data on 1.5-year OS were available for only three trials.[8,17,54] The 1.5-year OS rates were 47.8% (118/247) and 42.3% (163/385) in the combination therapy and control groups, respectively. The estimated pooled RR for the three trials exhibited significant improvements (fixed effects model: RR=1.45 [95% CI=1.24–1.71], *P*=0.02; random effects
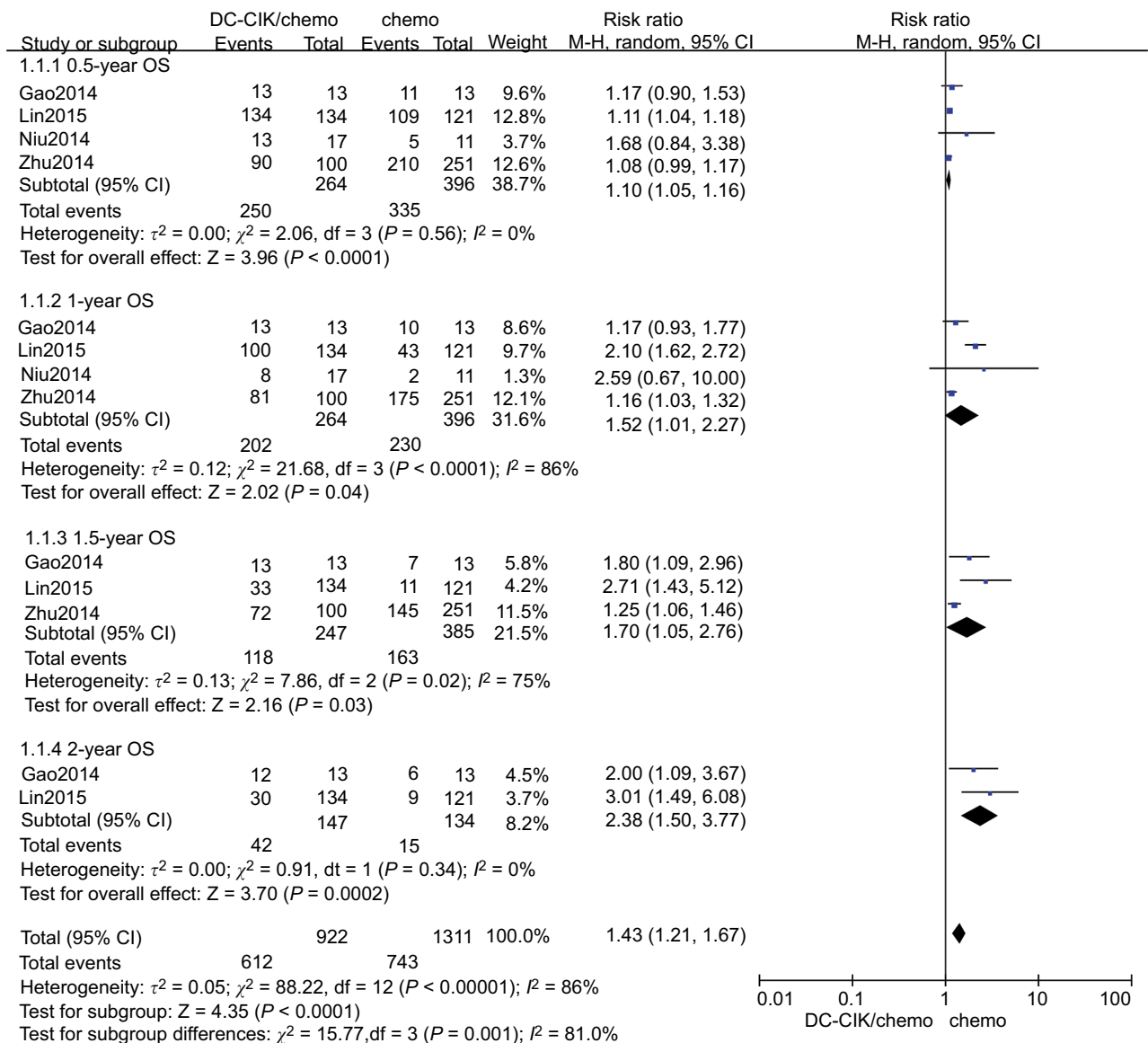
Study or subgroup	DC-CIK/chemo Events	Total	chemo Events	Total	Weight	Risk ratio M-H, random, 95% CI
1.1.1 0.5-year OS						
Gao2014	13	13	11	13	9.6%	1.17 (0.90, 1.53)
Lin2015	134	134	109	121	12.8%	1.11 (1.04, 1.18)
Niu2014	13	17	5	11	3.7%	1.68 (0.84, 3.38)
Zhu2014	90	100	210	251	12.6%	1.08 (0.99, 1.17)
Subtotal (95% CI)		264		396	38.7%	1.10 (1.05, 1.16)
Total events	250		335			
Heterogeneity: τ^2 = 0.00; χ^2 = 2.06, df = 3 (*P* = 0.56); I^2 = 0%						
Test for overall effect: Z = 3.96 (*P* < 0.0001)						
1.1.2 1-year OS						
Gao2014	13	13	10	13	8.6%	1.17 (0.93, 1.77)
Lin2015	100	134	43	121	9.7%	2.10 (1.62, 2.72)
Niu2014	8	17	2	11	1.3%	2.59 (0.67, 10.00)
Zhu2014	81	100	175	251	12.1%	1.16 (1.03, 1.32)
Subtotal (95% CI)		264		396	31.6%	1.52 (1.01, 2.27)
Total events	202		230			
Heterogeneity: τ^2 = 0.12; χ^2 = 21.68, df = 3 (*P* < 0.0001); I^2 = 86%						
Test for overall effect: Z = 2.02 (*P* = 0.04)						
1.1.3 1.5-year OS						
Gao2014	13	13	7	13	5.8%	1.80 (1.09, 2.96)
Lin2015	33	134	11	121	4.2%	2.71 (1.43, 5.12)
Zhu2014	72	100	145	251	11.5%	1.25 (1.06, 1.46)
Subtotal (95% CI)		247		385	21.5%	1.70 (1.05, 2.76)
Total events	118		163			
Heterogeneity: τ^2 = 0.13; χ^2 = 7.86, df = 2 (*P* = 0.02); I^2 = 75%						
Test for overall effect: Z = 2.16 (*P* = 0.03)						
1.1.4 2-year OS						
Gao2014	12	13	6	13	4.5%	2.00 (1.09, 3.67)
Lin2015	30	134	9	121	3.7%	3.01 (1.49, 6.08)
Subtotal (95% CI)		147		134	8.2%	2.38 (1.50, 3.77)
Total events	42		15			
Heterogeneity: τ^2 = 0.00; χ^2 = 0.91, dt = 1 (*P* = 0.34); I^2 = 0%						
Test for overall effect: Z = 3.70 (*P* = 0.0002)						
Total (95% CI)		922		1311	100.0%	1.43 (1.21, 1.67)
Total events	612		743			
Heterogeneity: τ^2 = 0.05; χ^2 = 88.22, df = 12 (*P* < 0.00001); I^2 = 86%						
Test for subgroup: Z = 4.35 (*P* < 0.0001)						
Test for subgroup differences: χ^2 = 15.77, df = 3 (*P* = 0.001); I^2 = 81.0%						

Risk ratio
M-H, random, 95% CI

0.01   0.1   1   10   100
DC-CIK/chemo   chemo

Figure 2 Forest plot of the comparison of OS (random effects).
Note: A random-effects meta-analysis model (M-H method) was used for evaluation.
Abbreviations: DC-CIK/chemo, DC-CIK immunotherapy combined with chemotherapy; Chemo, chemotherapy alone; OS, overall survival.
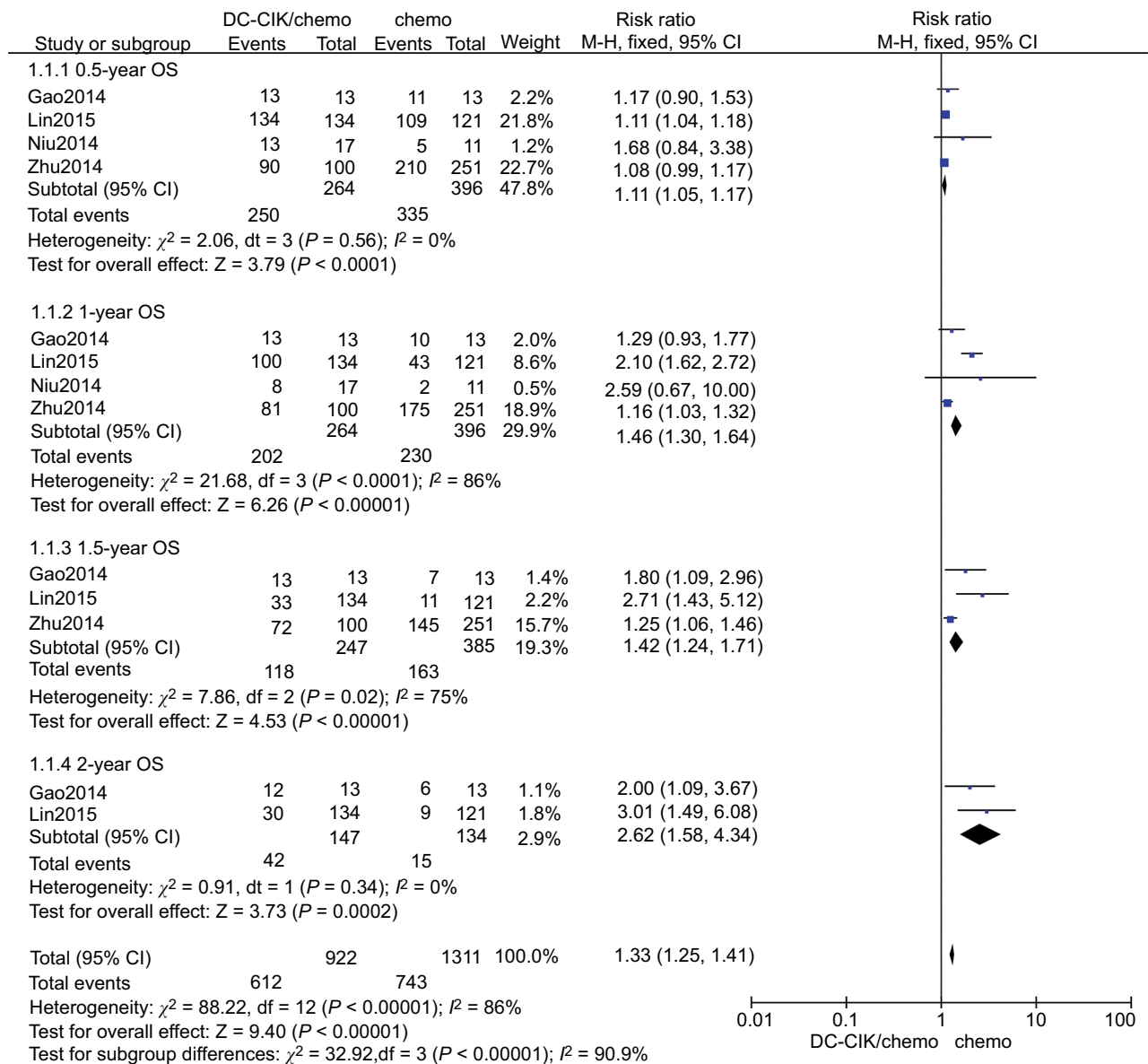
Figure 3 Forest plot of the comparison of OS (fixed effects).
Note: A fixed effects meta-analysis model (M-H method) was used for evaluation.
Abbreviations: DC-CIK/chemo, DC-CIK immunotherapy combined with chemotherapy; Chemo, chemotherapy alone; OS, overall survival.

model: RR=1.70 [95% CI=1.05–2.76], P=0.030). We found statistically significant heterogeneity in the three trials (χ^2=7.86, df=2, P=0.02, I^2=75%) (Figures 2 and 3).

Two-year OS

Data on 2-year OS were available for two trials.[8,17] The 2-year OS rate was 28.6% (42/147) in the combination therapy group and 11.2% (15/134) in the control group. The estimated pooled RR for the two trials demonstrated that DC-CIK cell therapy significantly improved the 2-year

OS in CRC patients (fixed effects model: RR=2.62 [95% CI=1.58–4.34], P=0.0002; random effects model: RR, 2.38 [95% CI=1.50–3.77]; P=0.0002). We did not detect statistically significant heterogeneity in the two trials ((χ^2=0.91, df=1, P=0.34, I^2=0%) (Figures 2 and 3).

To determine the differences in OS between the combination therapy and control groups, mean OS rates and the result of paired t-tests of included studies are shown in Figure 4, with a P-value of 0.025, indicating that DC-CIK cell therapy significantly improved OS rates in patients with CRC.

Six-month DFS

Data on 6-month DFS were available for two trials.[8,25] The 6-month DFS rates were 59.8% (52/87) and 38.5% (55/143) in the combination therapy and control groups, respectively. The combined RR (fixed effects model: RR=1.46 [95% CI=1.13–1.89], *P*=0.004; random effects model: RR=1.40 [95% CI=1.12–1.75]; *P*=0.004) indicated that DC-CIK cell therapy combined with chemotherapy was markedly effective in terms of its effect on DFS. We found no statistical heterogeneity in the two trials (χ^2=0.70, df=1, *P*=0.40, I^2=0%) (Figures 5 and 6).
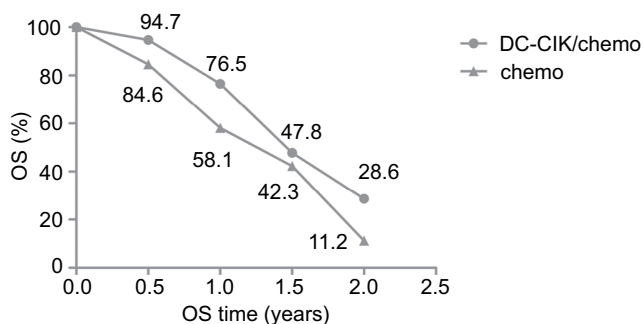
Figure 4 Mean survival curve for the combination therapy (DC-CIK/chemo) and control (chemo) groups.
Notes: A paired *t*-test was used for statistical analysis (*P*=0.025; *P*-values less than 0.05 were considered significant).
Abbreviations: DC-CIK/chemo, DC-CIK immunotherapy combined with chemotherapy; chemo, chemotherapy alone; OS, overall survival.

One-year DFS

Data on 1-year DFS were available for two trials.[8,25] The 1-year DFS rates were 33.3% (29/87) and 14.7% (21/143) in the combination therapy and control groups, respectively. When we used a fixed effects model for analysis, we found that the combination therapy could prolong 1-year DFS (fixed effects model: RR=1.86 [95% CI=1.24–2.80], *P*=0.003). However, when a random effects model was used for analysis, there was no significant difference between the two groups in 1-year DFS (random effects model: RR=1.72 [95% CI=0.95–3.31]; *P*=0.07). We did not find statistical heterogeneity in the two trials ((χ^2=2.42, df=1, *P*=0.12, I^2=59%) (Figures 5 and 6).

To determine the differences in DFS between the combination therapy and control groups, mean DFS rates and the results of paired *t*-tests of included studies are shown in Figure 7, with a *P*-value of 0.043, indicating that DC-CIK cell therapy significantly improved DFS in patients with CRC.

Adverse effects

None of the study patients had any severe adverse effects due to their treatment. The proportion of fever in the combination therapy group was higher than that in the control group, and the transfusion of DC vaccine and CIK cells has been thought to be the main reason. Most of the patients with fever in our study had temperatures ranging from 37.5°C to 40.0°C, and the fever was resolved spontaneously without
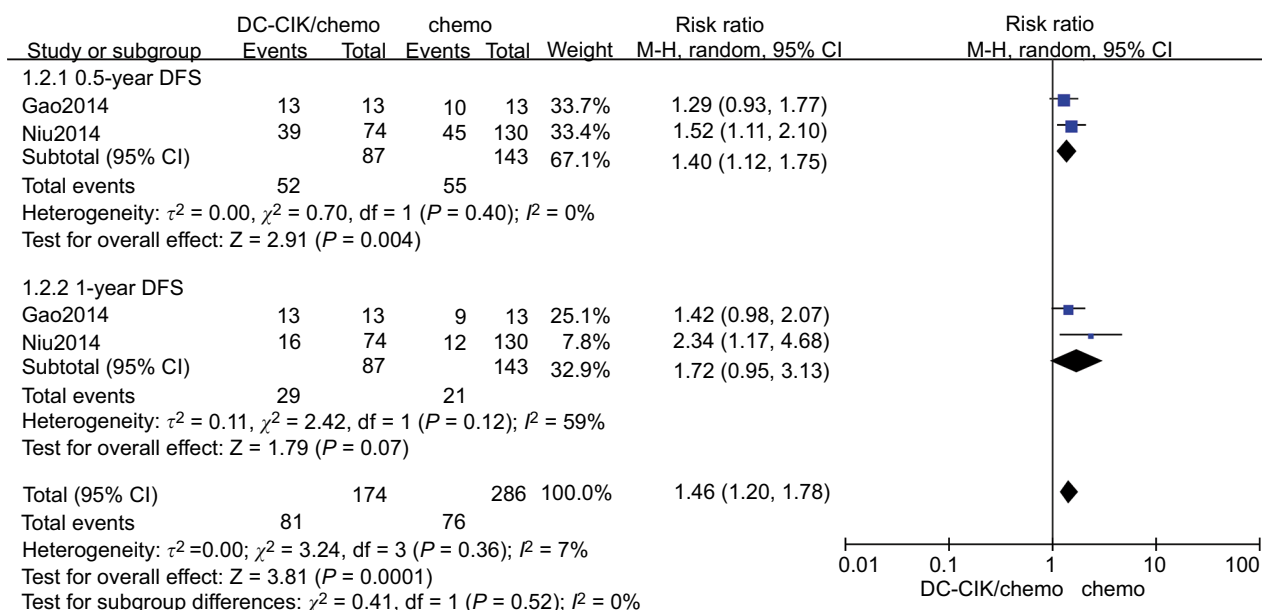

Figure 5 Forest plot of the comparison of DFS (random effects).
Note: A random-effect meta-analysis model (M-H method) was used for evaluation.
Abbreviations: DC-CIK/chemo, DC-CIK immunotherapy combined with chemotherapy; Chemo, chemotherapy alone; DFS, disease-free survival.
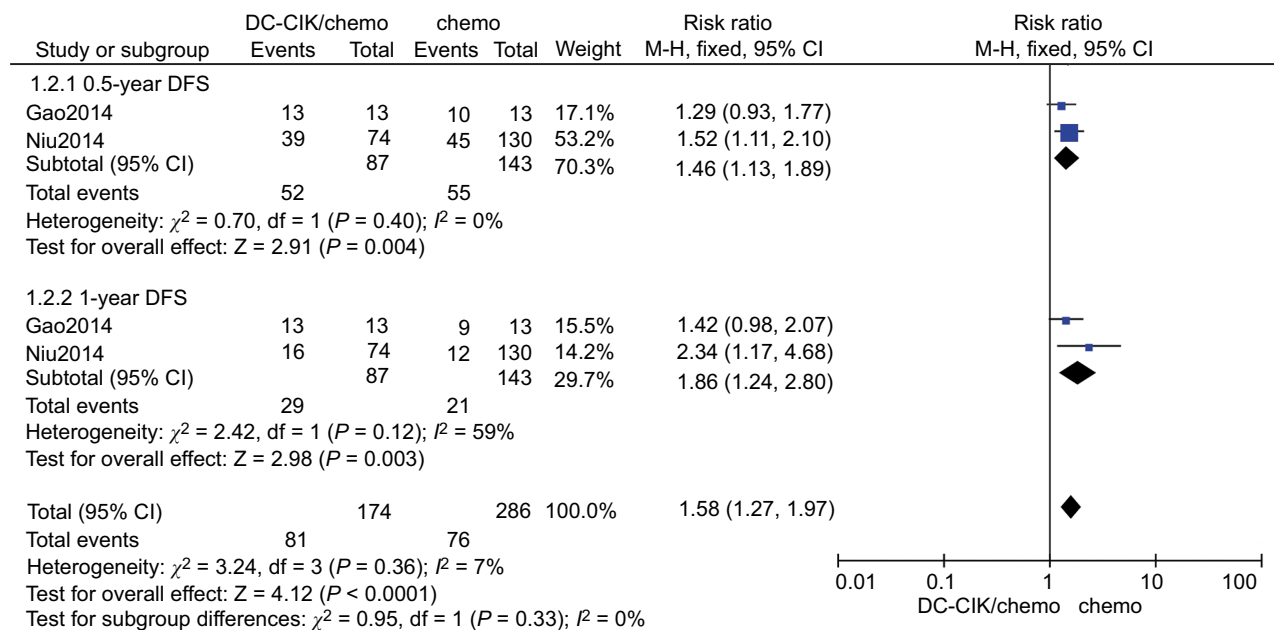
Study or subgroup	DC-CIK/chemo Events	Total	chemo Events	Total	Weight	Risk ratio M-H, fixed, 95% CI	Risk ratio M-H, fixed, 95% CI
1.2.1 0.5-year DFS							
Gao2014	13	13	10	13	17.1%	1.29 (0.93, 1.77)	
Niu2014	39	74	45	130	53.2%	1.52 (1.11, 2.10)	
Subtotal (95% CI)		87		143	70.3%	1.46 (1.13, 1.89)	
Total events	52		55				
Heterogeneity: $\chi^2 = 0.70$, df = 1 ($P = 0.40$); $I^2 = 0\%$							
Test for overall effect: Z = 2.91 ($P = 0.004$)							
1.2.2 1-year DFS							
Gao2014	13	13	9	13	15.5%	1.42 (0.98, 2.07)	
Niu2014	16	74	12	130	14.2%	2.34 (1.17, 4.68)	
Subtotal (95% CI)		87		143	29.7%	1.86 (1.24, 2.80)	
Total events	29		21				
Heterogeneity: $\chi^2 = 2.42$, df = 1 ($P = 0.12$); $I^2 = 59\%$							
Test for overall effect: Z = 2.98 ($P = 0.003$)							
Total (95% CI)		174		286	100.0%	1.58 (1.27, 1.97)	
Total events	81		76				
Heterogeneity: $\chi^2 = 3.24$, df = 3 ($P = 0.36$); $I^2 = 7\%$							
Test for overall effect: Z = 4.12 ($P < 0.0001$)							
Test for subgroup differences: $\chi^2 = 0.95$, df = 1 ($P = 0.33$); $I^2 = 0\%$							

0.01   0.1   1   10   100
DC-CIK/chemo   chemo

Figure 6 Forest plot of the comparison of DFS (fixed effects).
Note: A fixed effects meta-analysis model (M-H method) was used for evaluation.
Abbreviations: DC-CIK/chemo, DC-CIK immunotherapy combined with chemotherapy; Chemo, chemotherapy alone; DFS, disease-free survival.
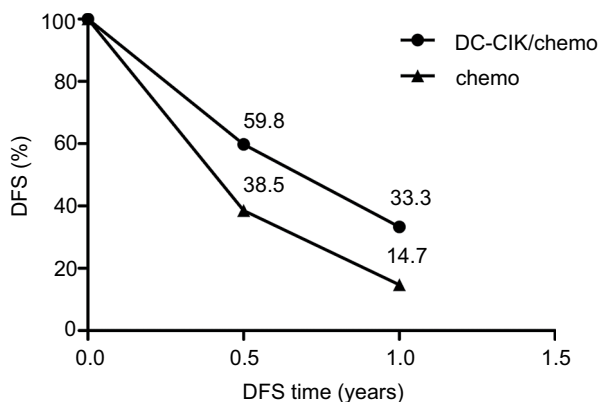
Figure 7 Mean DFS rates in the combination therapy (DC-CIK/chemo) and control (chemo) groups.
Notes: A paired t-test was used for statistical analysis ($P=0.043$; P-values less than 0.05 were considered significant).
Abbreviations: DC-CIK/chemo, DC-CIK immunotherapy combined with chemotherapy; Chemo, chemotherapy alone; DFS, disease-free survival.

any treatment in most patients, except some who received antipyretic treatment. There were no significant differences between the two groups in the incidence of other adverse effects, such as insomnia, anorexia, joint soreness, skin rash, or leukopenia (Table 2).

Discussion

In recent years, immunotherapy has become the most promising approach for cancer therapy.[3] CIK cell therapy is a subset of immunotherapy that has attracted more and more attention due to its strong antitumor activity.[39] The combination of DC vaccine and CIK cells can enhance the antitumor response, and this combination therapy made satisfying achievements in clinical applications of various tumors. A randomized controlled study reported that 1-year OS and DFS rates in gastric cancer and CRC patients who received DC vaccine and CIK cell therapy combined with chemotherapy were significantly higher than those in patients who received chemotherapy alone.[8] Furthermore, a recent meta-analysis included randomized controlled trials (RCTs) which applied chemotherapy with and without DC-CIK (DCs co-cultured with CIK cells before infusion or infusion of DC vaccine and CIK cells, respectively), and demonstrated that the combination therapy can markedly improve 2- and 3-year OS as well as 1- and 3-year DFS rates over chemotherapy alone for solid tumors, such as non-small-cell lung cancer, breast cancer, and gastrointestinal cancer. In addition, the combination therapy has been more effective for gastrointestinal cancers than for non-small-cell lung cancer in terms of OS.[14]

This meta-analysis focused on chemotherapy combined with DC vaccine and CIK in CRC treatment. Considering that the quality of published literature may lead to bias of the meta-analysis, we enrolled four relatively high-quality clinical trials that were published in English and met the inclusion criteria. We used both random and fixed effects models for statistical analysis so that the results would be

Table 2 Adverse effects after DC vaccine and CIK cell therapy combined with chemotherapy

Study	Combined therapy	Chemotherapy only
Gao et al[8]	Fever (33%)	Unknown
	Anorexia (53.73%)	Anorexia (96.69%)
	Leukopenia (43.28%)	Leukopenia (80.17%)
Lin et al[17]	Thrombocytopenia (43.28%)	Thrombocytopenia (84.47%)
	Nausea, vomiting (58.21%)	Nausea, vomiting (58.21%)
	Abnormal liver function (41.04%)	Abnormal liver function (70.25%)
	Fever (38.57%)	
	Insomnia (47.14%)	
Niu et al[25]	Anorexia (38.57%)	Unknown
	Joint soreness (4.29%)	
	Skin rash (11.43%)	
	Fever (29.5%)	
	Insomnia (19.2%)	
Zhu et al[54]	Anorexia (9.1%)	Unknown
	Joint soreness (5.4%)	
	Skin rash (1%)	

more objective and reliable. Our analysis found that the combination treatment had favorable results for 6-month, 1-year, 1.5 year, and 2-year OS, and 6-month DFS in both the fixed and random effects models. However, no significant difference was found in the random effects model analysis of 1-year DFS. Data on 1-year DFS were available for only two trials, and these trials had small samples, which may affect the results. Therefore, more trials about DC vaccine and CIK cell treatment in CRC are needed to evaluate DFS in the future.

CIK cell-based immunotherapy is effective for metastatic CRC, as demonstrated by improved OS and progression-free survival rates.[16,52] Moreover, researchers have demonstrated that the infusion of DC vaccine and CIK cells can induce a strong immune response with a positive response of delayed-type hypersensitivity (DTH) in cancer patients, such as those with advanced renal cell carcinoma, hepatocellular carcinoma, and pancreatic cancer.[45,50]

The superior therapeutic effect of DC vaccine and CIK cell therapy over that of chemotherapy alone may be explained by three factors. First, cancer stem cells, which are resistant to chemotherapy and radiotherapy, and target proliferating cells, have the abilities of self-renewal, cancer initiation, and further maintenance of tumors. Since proliferation is not a prerequisite for the identification and destruction of tumor cells by immune mechanisms, DC vaccine and CIK cell therapy may be an effective way to eliminate cancer stem cells.[26] Second, CIK cells, which have the benefits of T lymphocytes and natural killer cells, exhibit strong antitumor activity, but not major histocompatibility

complex restriction.[28,31] This was demonstrated by higher serum IL-12 and IFN-γ levels in the combination group than in the chemotherapy-alone group, as reported by Gao et al,[8] indicating that CIK cell therapy may specifically promote a Th1 immune response to kill tumor cells. Third, combining with DC vaccine increases the antitumor activities of CIK cell therapy, both in theory and in practice.[4,5,44,48]

A higher incidence of fever was observed in the combination therapy group than that in the control group, and the transfusion of DC vaccine and CIK cells has been thought to be the main reason and, at the same time, may indicate a strong immune response. The frequencies of other treatment-related side effects, such as leukopenia, anemia, nausea, vomiting, and abnormal liver function, seem to be lower in the combination group compared with the control group, indicating that the infusion of DC vaccine and CIK cells is safe for patients with CRC.

Our meta-analysis has some limitations that may affect interpretation of the results. First, no statistical analysis about side effects was performed due to the limited data. Second, data on DFS were only available for two trials, which may have led to bias. Third, we reconstructed data from published articles rather than using the original records of the respective experiments, which may have led to deviation from the real data. Fourth, limited to research data, we just compared DC vaccine and CIK cells plus chemotherapy with chemotherapy alone, without the comparisons of DC vaccine plus chemotherapy, or CIK cells plus chemotherapy. Thus, we expect more related research to verify the safety and efficacy of DC vaccine and CIK cell therapy for CRC.

In conclusion, our analysis demonstrated that DC vaccine and CIK cell combination therapy was applicable for patients with CRC, which is a feasible choice to prolong survival and prevent tumor recurrence. This study may contribute to the widespread use of DC vaccine and CIK cells in CRC and provide valid evidence for the clinical application of other malignancies.

Acknowledgments

Author contributions

Haiqing Ma and Zhong Lin conceived and designed the experiments. Xiuling Zhou and Xiangqiong Mo performed the experiments. Shuncong Wang, Cuiling Zhou and Yonghui Su analyzed the data. Junlan Qiu and Jingjing Zhao contributed to the reagents, materials and analysis tools. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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