Int J Clin Exp Med 2017;10(6):8666-8676
www.ijcem.com /ISSN:1940-5901/IJCEM0034132

Review Article

The efficacy of combination of chemotherapy and cytokine-induced killer cells therapy for soft tissue cancer: a meta-analysis

Qiaoling Chen[1*], Yiguang Bai[2*], Dongqin Xiao[3], Kang Liu[3], Xiaocong Xiang[3], Gang Feng[3]

Departments of [1]Oncology, [2]Orthopaedics, Nanchong Central Hospital and The Second Clinical Institute of North Sichuan Medical University, Nanchong 637000, Sichuan, China; [3]The Research Institute Tissue Engineering and Stem Cells, Nanchong Central Hospital and The Second Clinical Institute of North Sichuan Medical University, Nanchong 637000, Sichuan, China. [*]Co-first authors.

Received June 21, 2016; Accepted August 19, 2016; Epub June 15, 2017; Published June 30, 2017

Abstract: Purpose: To assess the efficacy of combined therapy of chemotherapy and cytokine-induced killer (CIK) cells on treatment of multiple types of soft tissue tumors with overall survival (OS). Methods: Pooling all data together, we assessed the effect of combination of chemotherapy and CIK cells therapy on 1-year, 2-year, 3-year and 5-year OS. Similar subgroup was also performed on colorectal and gastric tumors. The overall odds ratio (OR) and its corresponding 95% confidence interval (95% CI) for each analysis were calculated, respectively. Results: For soft tissue cancer, the chemotherapy plus CIK cells therapy significantly improved the 2-year, 3-year and 5-year OS (2-year: OR=1.19, 95% CI: 1.01-1.41, P=0.039; 3-year: OR=1.35, 95% CI: 1.19-1.54, P=0.000; 5-year: OR=1.86, 1.32-2.63, P=0.000), indicating better survivals occurred with the adjuvant CIK cells therapy 2 years, 3 years and 5 years after treatment compared to the conventional chemotherapy alone. We performed the subgroup analysis in colorectal and gastric tumors, the combination of chemotherapy and CIK cells therapy significantly improved the 5-year OS (OR=1.77, 95% CI: 1.25-2.51, P=0.001) for gastric cancer patients with the chemotherapy plus CIK cells treatment, whereas for colorectal cancer, it could not be improved after the combination therapy. Conclusion: The combination of chemotherapy and CIK cells treatment improves the OS for patients with soft tissue cancer, especially for gastric cancer patients. The combined therapy of chemotherapy and CIK cells treatment should be recommended for patients with multiple types of soft tissue tumors.

Keywords: Chemotherapy, CIK cells therapy, soft tissue cancer, meta-analysis, cytokine-induced

Introduction

Soft tissue cancer whose family is composed of gastrointestinal stromal tumor, soft tissue sarcoma and desmoid-type fibromatosis can arise in various soft tissues and a variety of body sites[1].Gastric cancer, a kind of soft tissue cancer, which is the most common cancer in the Asian-Pacific region with approximate 1.2 million new cases and 609,051 deaths annually, has poor prognosis and is resistant to chemo- and/or radiotherapy [2]. Colorectal cancer is the third most commonly diagnosed cancer in humans. As dietary habits have changed in recent years, the number of cases of colon cancer has increased faster in the Eastern world [3, 4]. Surgical resection with or without adjuvant chemo- and/or radiation therapy remains the important modality for both gastric and colorectal cancers. However, limited clinical benefits were observed, since high rate of tumor metastasis and severe side effects usually limit the efficacy of this anticancer modality, even if current adjuvant chemo-radiation therapy has been shown to extend patient survival in the presence of recurrent lesions [5, 6].

Recently, a variety of immunotherapeutic approaches, which are aimed to trigger an antitumor immune response, promote the bodies' abilities of recognition and then kill cancer cells by stimulating patients' immune system, have emerged as adjuvant or even alternative therapies for cancer treatment [7]. Among all the immunotherapies, the cellular immunotherapeutic approach using cytokine-induced killer (CIK) cells has been regarded as a promising

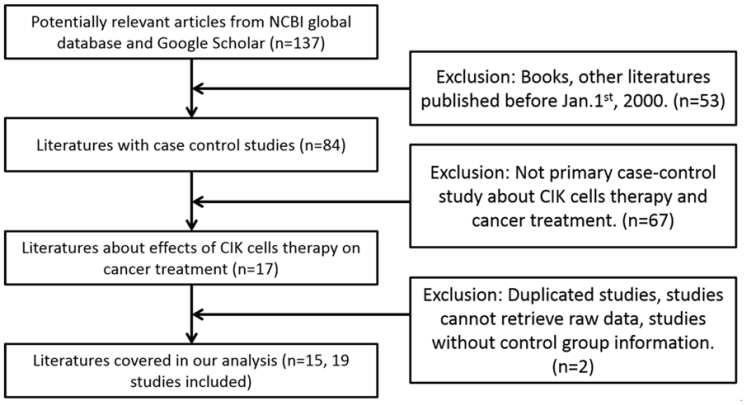

Figure 1. Flow diagram of literature search.

intervention [7]. CIK cells are capable of co-expressing CD3, CD56 and expansion in culture, which are phenotypic and functional hallmarks of T cells, and not requiring functional priming for in vivo activity, similar to natural killer cells [8]. CIK cells possess a stronger anti-tumor activity and a broader target tumor spectrum than the reported anti-tumor effector cells [9]. CIK cells also exhibit enhanced tumor cell lytic activity [10], higher proliferation rate [11] and relatively lower toxicity [9].

Although passive immunotherapy of CIK cells has been proved to be positive in soft tissue cancer treatment, the results are still inconsistent. Study from Wu et al. reported that after treating with the combination of chemotherapy plus autologous CIK cells, the advanced non-small cell lung cancer patients had a better quality of life, higher disease control rate, longer time to progression and overall survival than those treated with chemotherapy alone [12]. A randomized controlled study, performed by Shi et al. was to investigate the efficacy of erlotinib plus dendritic cells and cytokine-induced killer cells on advanced non-small cell lung cancer, and their results suggested that no significant difference in overall survival was observed between dendritic cells/cytokine-induced killer plus erlotinib and erlotinib therapy alone [13]. In current meta-analysis, our purpose was to investigate the efficacy of chemotherapy plus CIK cells therapy on treatment of soft tissue cancer including gastric cancer, colorectal cancer, lung cancer, ovarian cancer, breast cancer and hepatocellular cancer with overall survival (OS) as the endpoint.

Materials and methods

Search strategy

For the first-round search, literatures were retrieved from NCBI Global Cross-database, including PubMed, PMC, Gene, etc, as well as Google Scholar using "cytokine induced killer cells", "CIK cells treatment", "gastric cancer", "colorectal cancer", "lung cancer", "ovarian cancer", "breast cancer" and "hepatocellular cancer" and "soft tissue cancer" as key words. Then literatures which were not aimed at investigating association between CIK cells treatment and soft tissue cancer were removed. We also excluded literatures without comprehensive statistical information or impossible to retrieve the original data. For studies covered in each article overlapped, we only kept the ones showed the most extensive information. Some article types such as letters, meetings and reviews were also eliminated.

Data extraction

The potential eligible papers were evaluated by two independent authors and the following information was extracted from the covered studies: the first author, the year of publication, mean age in CIK and control groups, cancer type, tumor stage, previous treatment method, the number of CIK cells, the administration approach and the number of patients with different overall survival in both case group treated with combined therapy of chemotherapy and CIK cells therapy and control group treated with chemotherapy alone.

Statistical analysis

For entire database, four analyses were performed stratified by the follow-up period including 1-year, 2-year, 3-year and 5-year. The OS was evaluated in the 4 subgroup analysis, and OR was generated accordingly to investigate the effect of combined therapy of chemotherapy and CIK cells therapy on soft tissue cancer. Overall survival number and total number of patients in conventional chemotherapy group were served as reference for the generation of corresponding OR and 95% CI. Similar

Table 1. Characteristics of each included studies

Study	Mean age		Cancer type	Tumor stage	Previous treatment	CIK cell number	Administration
	CIK	Ctrl					
Jiang, 2006	53	53	Gastric	IV	Gastrectomy	1×10^9	Transfusion
Jiang, 2010	59.9	59.9	Gastric	I, II, III, IV	Chemo	1×10^9	Transfusion
Shi, 2012	57	57	Gastric	III, IV	5-FU	1×10^9	Transfusion
Liu, 2013	55.7	55.7	Gastric	I, II, III, IV	5-HT	1×10^9	Transfusion
Gao, 2014	63.02	63.02	Gastric	I, II, III, IV	NA	58×10^8	Infusion
Wei, 2009	55.5	54	Colon	I, II, III	NA	1×10^{10}	NA
Cai, 2010	44.5	46.7	Colon	II, III	NA	NA	NA
Ying, 2010	NA	NA	Colon	II, III	NA	1×10^{10}	NA
Li, 2012	57.5	54.5	Colon	II, III	NA	NA	NA
Zhang, 2011	NA	NA	Colon	II, III, IV	NA	1×10^9	NA
Zhu, 2011	68.3	59.2	Colon	II, III, IV	NA	1×10^{10}	NA
Wu, 2008	60	61	Lung	III, IV	Chemo	1×10^9	Transfusion
Jin, 2014	53.66	52.95	Lung	I, II, III	Chemo	NA	Infusion
Shi, 2014	59.5	62.5	Lung	III, IV	Chemo	1×10^6	Transfusion
Liu, 2014	52	53.5	Ovarian	II, III, IV	Chemo	11.8×10^9	Transfusion
Pan, 2014	50	51	Breast	I, II, III	Surgery	1×10^8	Transfusion
Pan, 2013	49.16	62.5	HCC	I, II, III	NA	1×10^{10}	Transfusion
Zhao, 2015	NA	NA	Renal	I, II	Combined	1×10^7	NA
Zhang, 2014	NA	NA	Colon	I, II, III, IV	5-FU	5×10^8	Transfusion

subgroup analyses were conducted on gastric cancer database and colorectal cancer database as well due to the large number of included studies. Specifically, based on the available data, 1-year, 2-year and 3-year follow-up OS were analyzed for colorectal cancer while 1-year, 3-year and 5-year follow-up OS were analyzed for gastric cancer. An OR larger than 1 indicated higher survival rate, and concluded a lower recurrence or a longer survival period occurred in the combined therapy of chemotherapy and CIK cells therapy (case group). *P* value smaller than 0.05 signified a statistical difference existed between control and case groups.

In order to choose a suitable analysis model for the calculation of OR and 95% CI, we firstly tested the heterogeneity inter pooled studies using I^2 index. when I^2 index was less than 50%, we considered no significant heterogeneity between pooled data and the Mantel-Haenszel (M-H) fixed-effects model was adopted for the calculation of OR and 95% CI. Otherwise, the DerSimonian and Laird (D-L) random-effects model was used. The available OS data were analyzed with the STATA 12 software (STATA Corp LP, College Station, Texas, United States). Forest plots were generated to summarize the results. Both Begg's test and Egger's test were used to examine the publication bias.

Results

Study characteristics

A total of 135 literatures were collected from NCBI Global Cross-database and Google Scholar after the first round search. 53 books, reviews and meetings were excluded, leaving 82 literatures containing case-control studies. Then we eliminated 67 papers not regarding CIK cells therapy and cancer treatment. Eventually, we included 19 studies covered in 15 articles [14-28] for our meta-analysis after excluding duplications and studies without raw data or information of control group. The details of study selective and exclusive process were described in **Figure 1**. The main characteristics of all the 19 eligible studies were presented in **Table 1** and pooled data for meta-analysis were displayed in **Table 2**.

The effect of CIK cells treatment as an adjuvant therapy on the 1-year OS for soft tissue cancer

For 1-year OS of soft tissue cancer, 16 eligible studies were pooled and the results were

Table 2. Pooled Data for overall survival in combination of chemotherapy and cytokine-inducedkiller cells therapy group and conventional chemotherapy group

Study	Year	Cancer Type	CIK cells Treatment		Conventional Treatment	
			OS (%)	Total	OS (%)	Total
1-year OS						
Jiang, 2006	2006	Gastric	16 (51.0)	32	12 (48.0)	25
Shi, 2012	2012	Gastric	73 (98.0)	74	73 (95.0)	77
Liu, 2013	2013	Gastric	50 (98.0)	51	44 (93.6)	47
Gao, 2014	2014	Gastric	25 (93.0)	27	21(79.0)	27
Wei, 2009	2009	Colon	41 (100)	41	81 (98.8)	82
Cai, 2010	2010	Colon	37(92.5)	40	35 (87.5)	40
Zhang, 2011	2011	Colon	31 (96.9)	32	28 (90.3)	31
Zhu, 2011	2011	Colon	28 (70.0)	40	10 (23.3)	43
Li, 2012	2012	Colon	20 (100)	20	19 (95.0)	20
Wu, 2008	2008	Lung	20 (68)	29	14 (47.0)	30
Shi, 2014	2014	Lung	6 (25)	26	3 (18.0)	28
Jin, 2014	2014	Lung	402 (97.8)	411	491 (92.3)	532
Liu, 2014	2014	Ovarian	46 (100)	46	46 (100)	46
Pan, 2014	2014	Breast	45 (100)	45	43 (95.6)	45
Pan, 2013	2013	Hepatocellular	191 (93.6)	204	165 (80.0)	206
Zhang, 2014	2014	Colon	29 (97)	30	29 (97)	30
2-year OS						
Jiang, 2006	2006	Gastric	13 (40.0)	32	9 (38.0)	25
Jiang, 2010	2010	Gastric	55 (73.5)	75	43 (52.6)	81
Liu, 2013	2013	Gastric	47 (92.2)	51	37 (78.7)	47
Wei, 2009	2009	Colon	38 (92.7)	41	68 (82.9)	82
Ying, 2010	2010	Colon	47 (92.2)	51	44 (86.3)	51
Zhang, 2011	2011	Colon	28 (87.5)	32	26 (83.9)	31
Zhu, 2011	2011	Colon	8 (20.0)	40	3 (7.0)	43
Li, 2012	2012	Colon	19 (95.0)	20	16 (80.0)	20
Liu, 2014	2014	Ovarian	46 (100)	46	44 (95.0)	46
Pan, 2014	2014	Breast	45 (100)	45	40 (88.6)	45
Pan, 2013	2013	Hepatocellular	170 (83.3)	204	143 (69.2)	206
Wu, 2008	2008	Lung	9 (30.0)	29	5 (18.0)	30
Zhang, 2014	2014	Colon	27 (92)	30	25 (83)	30
3-year OS						
Jiang, 2006	2006	Gastric	4 (11.0)	32	3 (12.0)	25
Shi, 2012	2012	Gastric	50 (67.7)	74	42 (54.5)	77
Liu, 2013	2013	Gastric	37 (72.5)	51	28 (59.6)	47
Zhao, 2013	2013	Gastric	33 (62.3)	53	52 (46.4)	112
Gao, 2014	2014	Gastric	22(82.0)	27	11 (42.0)	27
Wei, 2009	2009	Colon	30 (73.2)	41	46 (56.1)	82
Cai, 2010	2010	Colon	30 (75.0)	40	25 (83.3)	30
Ying, 2010	2010	Colon	45 (88.2)	51	35 (68.6)	51
Jin, 2014	2014	Lung	275 (66.9)	411	237 (44.5)	532
Liu, 2014	2014	Ovarian	39 (86.1)	46	38 (83.3)	46
Pan, 2014	2014	Breast	44 (96.7)	45	34 (76.3)	45
Pan, 2013	2013	Hepatocellular	156 (76.6)	204	127 (61.6)	206
Zhang, 2014	2014	Colon	27 (92)	30	18 (62)	30
Zhao, 2015	2015	Renal	15 (48.8)	31	6 (21.2)	31
5-year OS						
Jiang, 2010	2010	Gastric	30 (40.4)	75	19 (23.9)	81
Shi, 2012	2012	Gastric	24 (32.4)	74	18 (23.4)	77
Zhao, 2013	2013	Gastric	30 (56.6)	53	30 (26.8)	112
Gao, 2014	2014	Gastric	18 (66.0)	27	9 (34.0)	27
Jin, 2014	2014	Lung	114 (27.7)	411	49 (9.2)	532
Pan, 2013	2013	Hepatocellular	134 (65.9)	204	103 (50.2)	206

shown in **Table 3**. No significant heterogeneity was detected (I^2=0.0%), and the fixed-effects model was adopted to calculate its overall OR and corresponding 95% CI. Although the overall OR was 1.11 (95% CI: 0.99-1.25, **Figure 2**), there was no significant difference in the 1-year OS (P=0.087) between the control group treated with chemotherapy alone and the case group treated with combination of chemotherapy and CIK cells therapy, which indicated that for patients with soft tissue cancer, the adjuvant therapy of CIK cells would not significantly improve the 1-year OS.

The effect of CIK cells treatment as an adjuvant therapy on the 2-year OS for soft tissue cancer

There were 13 included studies to analyze the efficacy of combination of chemotherapy and cytokine-induced killer cells therapy on 2-year OS for patients with soft tissue cancer. The fixed-effects model was selected for the calculation of overall OR and corresponding 95% CI due to no significant heterogeneity existed (I^2=0.0%) and the results were displayed in **Table 3**. The overall OR was estimated to be 1.19 (95% CI: 1.01-1.40, P=0.039, **Figure 3**), suggesting that the 2-year OS was significantly higher in combined therapy group than that in chemotherapy alone.

The effect of CIK cells treatment as an adjuvant therapy on the 3-year OS for soft tissue cancer

Totally 14 eligible case-control studies were pooled for

Table 3. Meta-analysis for entire database with 1, 2, 3 and 5-year OS

Period	Analysis Method	Heterogeneity		OR				Publication Bias	
		I^2 (%)	*p*-value	Overall	Lower	Upper	*p*-value	Begg	Egger
1-year OS	Fixed	0	0.941	1.11	0.99	1.25	0.087	0.010	0.183
2-year OS	Fixed	0	0.995	1.19	1.01	1.40	0.039	0.300	0.270
3-year OS	Fixed	0	0.956	1.35	1.19	1.54	<0.0001	0.661	0.574
5-year OS	Random	59.6	0.030	1.86	1.32	2.63	0.0004	1.000	0.995

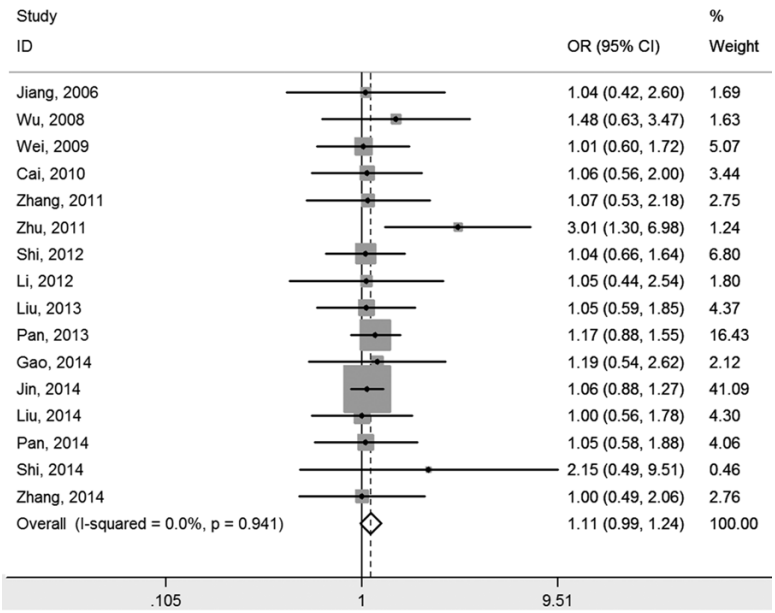

Figure 2. Forest plot of study evaluating the effect of CIK cells treatment as an adjuvant therapy on the 1-year OS for soft tissue cancer.

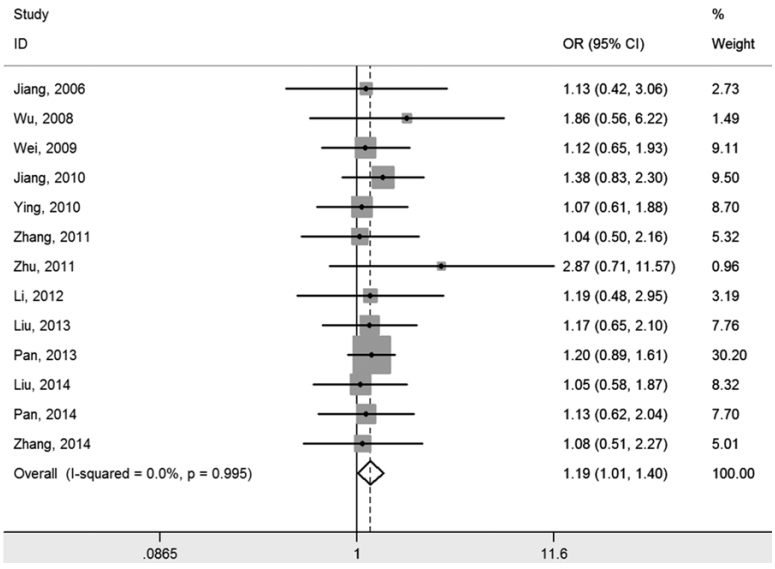

Figure 3. Forest plot of study estimating the effect of CIK cells treatment as an adjuvant therapy on the 2-year OS for soft tissue cancer.

this analysis and the results were displayed in **Table 3**. There was no significant heterogeneity inter-included studies (I^2=0.0%), so we chose the fixed-effects model to calculate overall OR and corresponding 95% CI. The overall OR was 1.35 (95% CI: 1.19-1.54, **Figure 4**) and the *p* value was lower than 0.05 (P=0.000), which revealed that significantly higher 3-year OS was detected in combined therapy than in chemotherapy alone.

The effect of CIK cells treatment as an adjuvant therapy on the 5-year OS for soft tissue cancer

In terms of the 5-year OS, 6 eligible studies were included to analyze the efficacy of combination of chemotherapy and CIK cells therapy on 2-year OS for patients with soft tissue cancer. The results were presented in **Table 3**, and the random-effects model was used for the calculation of overall OR and corresponding 95% CI due to the value of I^2 index (I^2=59.6%). Overall OR was estimated to be 1.86 (95% CI: 1.32-2.63, P=0.000, **Figure 5**), signifying that there was significant difference in 5-year OS between combined therapy and chemotherapy alone, and 5 years after treatment, the case group tre-

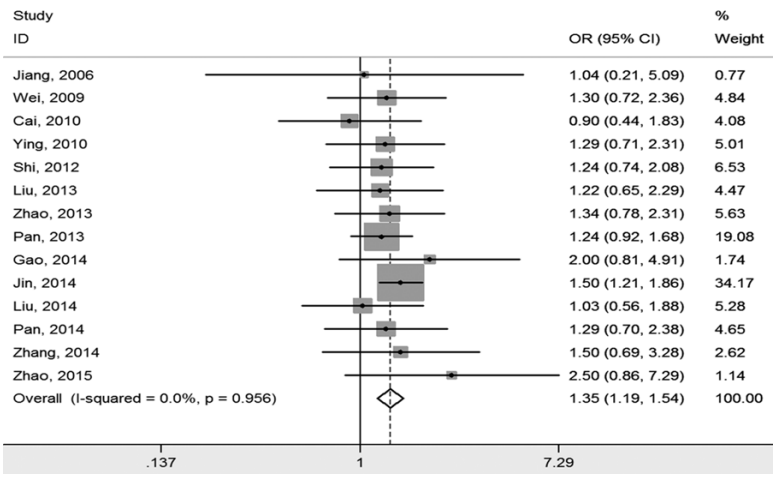

Figure 4. Forest plot of study assessing the effect of CIK cells treatment as an adjuvant therapy on the 3-year OS for soft tissue cancer.

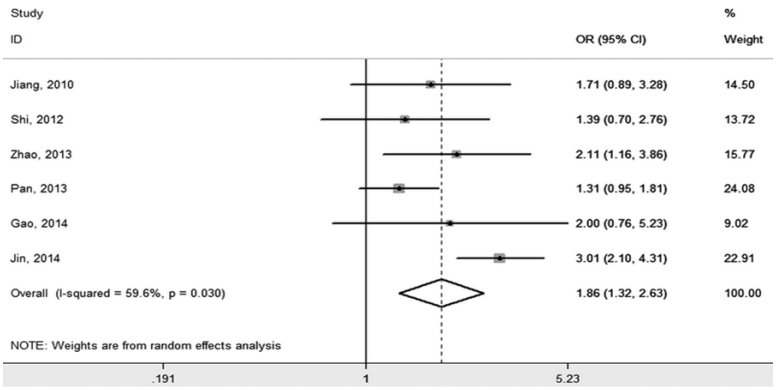

Figure 5. Forest plot of study evaluating the effect of CIK cells treatment as an adjuvant therapy on the 5-year OS for soft tissue cancer.

ated by combined therapy of chemotherapy and CIK cells therapy had more survivals.

The effect of CIK cells treatment as an adjuvant therapy on colorectal cancer

Subgroup analysis for colorectal cancer was performed and the results were shown in **Table 4**. Considering the low heterogeneity, the fixed-effects model was selected for the calculation of overall OR and corresponding 95% CI. The overall OR for 1-year, 2-year and 3-year OS were all larger than 1 (1-year OS: OR=1.18, 95% CI: 0.89-1.56, **Figure 6A**; 2-year OS: OR=1.15, 95% CI: 0.86-1.53, **Figure 6B**; 3-year OS: OR=1.23, 95% CI: 0.89-1.71, **Figure 6C**), and all the *p* values were higher than 0.05, demonstrating that when CIK cells treatment as an adjuvant therapy for colorectal cancer, the 1-year, 2-year and 3-year OS have not significantly improved.

The effect of CIK cells treatment as an adjuvant therapy on gastric cancer

Similar subgroup analysis was also conducted for gastric cancer and the results were presented in **Table 5**. The fixed-effects model was used to calculate overall OR and corresponding 95% CI for no significant heterogeneity existing. All the overall OR were higher than 1 (1-year OS: OR=1.06, 95% CI: 0.78-1.44, **Figure 7A**; 3-year OS: OR=1.33, 95% CI: 0.98-1.79, **Figure 7B**; 5-year OS: OR=1.77, 95% CI: 1.25-2.51, **Figure 7C**), and all the corresponding *p* values were larger than 0.05 except for *p* value of 5-year OS (P= 0.001), which implied that the adjuvant therapy of CIK cells would significantly improve the 5-year OS for patients with gastric cancer.

Publication bias

As for publication bias, the results (**Tables 3**-**5**) of Begg's test and Egger's test signified that there was no publication bias in the analysis.

Discussion

In the current meta-analysis, 19 eligible studies covering 1244 patients with combined treatment of chemotherapy and CIK cells therapy and 1411 participant with conventional chemotherapy were included to assess the efficacy of the combined therapy on treatment of soft tissue cancer with overall survival (OS) as the endpoint. For multiple types of soft tissue tumors, the results suggested that the conventional chemotherapy plus CIK cells therapy significantly improved the 2-year, 3-year and 5-year OS, and there were more survivals of patients with soft tissue cancer 2 years, 3 years and 5 years after treatment with

Table 4. Meta-analysis for colon cancer database with 1, 2, and 3-year OS

Period	Analysis Method	Heterogeneity		OR				Publication Bias	
		I^2 (%)	*p*-value	Overall	Lower	Upper	*p*-value	Begg	Egger
1-year OS	Fixed	9.7	0.354	1.18	0.89	1.56	0.249	0.133	0.304
2-year OS	Fixed	0	0.873	1.15	0.86	1.53	0.358	0.133	0.052
3-year OS	Fixed	0	0.790	1.23	0.89	1.71	0.214	0.734	0.901

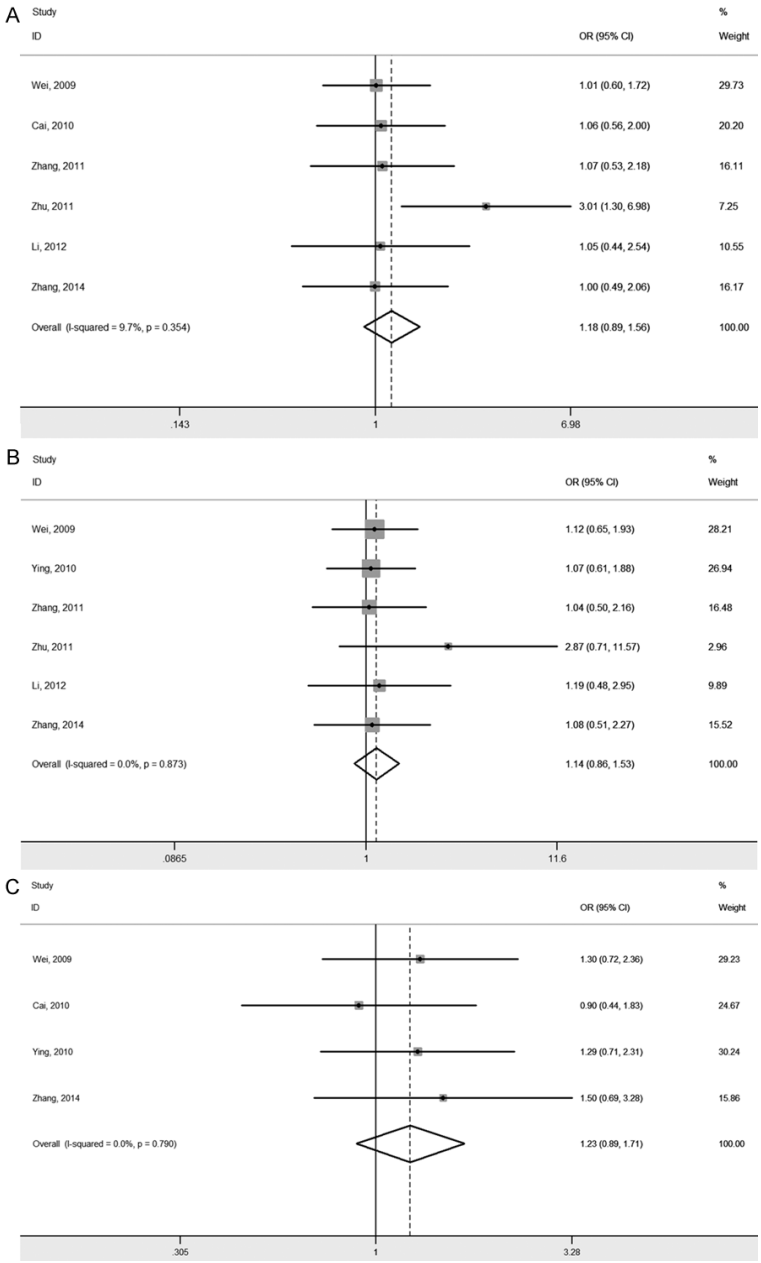

Figure 6. Forest plot of study assessing the effect of CIK cells treatment as an adjuvant therapy on colorectal cancer with 1-year OS (A), 2-year OS (B) and 3-year OS (C) as measures.

chemotherapy plus CIK cells therapy, compared to those in conventional chemotherapy group.

With respect to subgroup analysis of colorectal and gastric tumors, the results indicated that for gastric cancer, there were more survivals of patients 5 years after being treated with combined therapy of chemotherapy and CIK cells therapy than those treated with chemotherapy alone; whereas for colorectal cancer, the number of survivals after treatment in two groups was similar and the combined treatment of chemotherapy plus CIK cells therapy would not get more survivals, compared to conventional chemotherapy alone.

Accumulating reports revealed that the adoptive CIK cell transfer exhibited not only considerable antitumor efficacy with significantly improving progression-free and overall survival (OS) for some different types of tumors, but also no serious side effects and well tolerated by patients [7]. Amulticenter, randomized case-control study was performed to investigate the effect of adjuvant immunotherapy with autologous CIK cells on the recurrence-free survival and overall survival for patients with hepatocellular carcinoma (HCC), and the study documented that adjuvant immunotherapy with CIK cells increased recurrence-free and overall survival [29]. Aretrospective study performed by Pan et al. reported that for patients with triple-negative breast cancer, a combination of chemotherapy and

Table 5. Meta-analysis for gastric cancer database with 1, 3, and 5-year OS

Period	Analysis Method	Heterogeneity		OR				Publication Bias	
		I^2 (%)	*p*-value	Overall	Lower	Upper	*p*-value	Begg	Egger
1-year OS	Fixed	0	0.993	1.06	0.78	1.44	0.691	0.308	0.471
3-year OS	Fixed	0	0.905	1.33	0.98	1.79	0.064	0.806	0.765
5-year OS	Fixed	0	0.829	1.77	1.25	2.51	0.001	0.734	0.978

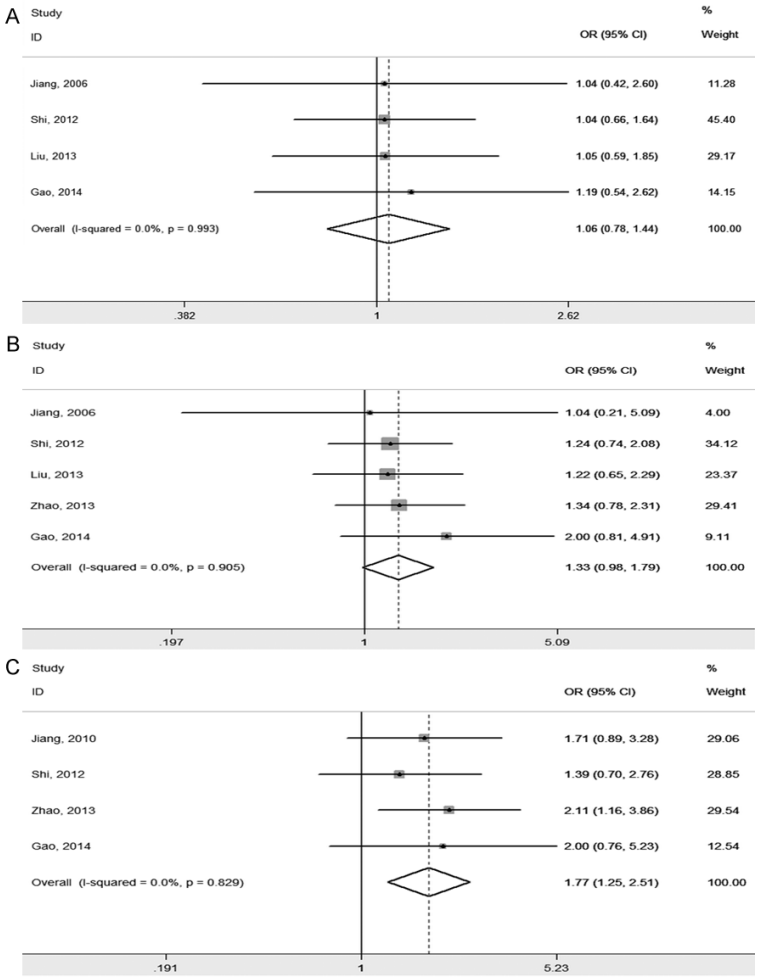

Figure 7. Forest plot of study estimating the effect of CIK cells treatment as an adjuvant therapy on gastric cancer with 1-year OS (A), 3-year OS (B) and 5-year OS (C) as measures.

CIK cells infusion was an effective therapeutic approach characterized by preventing disease recurrence and prolonging survival [23]. In order to assess the efficacy of CIK cells therapy for patients with advanced epithelial ovarian cancer after surgery followed by chemotherapy, Liu et al. performed a paired study and CIK cells therapy was considered to improve the progression-free survival with slight side effects after chemotherapy in their study [30]. Pooling all data together, our meta-analysis suggested that for soft tissue cancer, more survivals occurred in combined therapy of chemotherapy and CIK cells therapy than that in chemotherapy alone group.

With respect to the gastric cancer, a case-control study, published in 2013, was to evaluate the effect of CIK cells therapy combined with chemotherapy on the recurrence and survival rates for gastric cancer, and the results indicated that patients following combined therapy of CIK cells treatment and chemotherapy had significantly improved immune functions and significantly enhanced survival rates, compare with those following chemotherapy alone [31]. Study from Jiang et al. observed that for patients with gastric cancer, the survival rate within 2 years was higher in group treated with CIK cells plus chemotherapy than that of in group treated with chemotherapy alone, and after 2 years no difference was detected [16], and study from Shi et al. found that the adjuvant immunotherapy with CIK cells could not significantly improve the 5-year OS for gastric cancer patients [18], which were not consistent with our relevant results of subgroup analysis. However, in our meta-analysis with larger sample size by pooling all eligible studies together, which would increase the statistical power, we detected that the chemotherapy plus CIK cells therapy would significantly improve the 5-year OS but not the 1-year

and 3-year OS, which was consistent with studies from Jiang et al. [16] and Shi et al. [18].

In our study, we found that as for colorectal cancer, the combination of chemotherapy and CIK cells treatment had a null effect on the 2-year and 3-year OS, whereas the combined therapy could significantly improve the 2-year and 3-year OS for multiple soft tissue tumors when incorporating all data together. The reason for that might be the larger sample size of the overall analysis, especially, the case-control study performed by Pan et al. [24] possessed a relatively high weight (30.20%) in the overall analysis and might have an important effect on the result, in which 206 subjects with HCC were enrolled for the analysis and found that the combined therapy significantly improved the OS. For gastric cancer, the 3-year OS could not be improved by the combined treatment, which was inconsistent with that for overall analysis of multiple soft tis-sue tumors, and we speculated that the larger number of eligible studies included in the overall analysis should be partly responsible for the inconsistence, mainly, study from Jin et al. [21], which showed that the combined therapy significantly improved the OS for lung cancer patients, occupied a 34.17% weight and would heavily impact on the result of overall analysis.

To our knowledge, the present study is the first meta-analysis to investigate the efficacy of combination of chemotherapy and CIK cells therapy for multiple soft tissue tumors. However, there are several limitations. Firstly, the number of CIK cells given to patients was not exactly the same in all the 17 included studies, so we should take caution when interpret the results. Secondly, we only made the subgroup analysis of colorectal and gastric tumors, and with more relevant data available, subgroup analysis of other types of soft tissue cancer would be made. Additionally, unpublished papers and abstracts have not been considered in our meta-analysis, since the required data could not be retrieved.

Conclusion

Taken together, the current meta-analysis demonstrates that for soft tissue cancer patients, the combination of chemotherapy and CIK cells treatment significantly improve the 2-year, 3-year and 5-year OS, and more survivals occur in the combined therapy than in chemotherapy alone. Additionally, when CIK cells therapy is regarded as an adjuvant treatment for gastric cancer, the 5-year OS is significantly improved and more survivals occur 5 years after treatment. So the combined therapy of chemotherapy and CIK cells treatment should be recommended for patients with multiple types of soft tissue tumors.

Acknowledgements

This work is supported in part by the Science and Technology Bureau scientific research projects of Nanchong (KY-14A0022), the Research Program General Project of the Education Department of Sichuan Provincial (15ZB0201), the Research Development Program of North Sichuan Medical (CBY14-A-ZD02), the Education Department of Sichuan Provincial (15ZA0216) and the Focus Research Projects of and the Science and Technology Bureau Scientific Research Projects of Nanchong (KY-14A0017), the Research Development Program of North Sichuan Medical (CBY15-A-ZD02), and the Research Program Health and Family Planning Commission of Sichuan Province (16PJ202).

Disclosure of conflict of interest

None.

Address correspondence to: Gang Feng, The Research Institute Tissue Engineering and Stem Cells, Nanchong Central Hospital and The Second Clinical Institute of North Sichuan Medical University, 97th South Renmin Road, Shunqing District, Nanchong 637000, Sichuan, China. Tel: +86-0817-2258614; +86-15881729989; E-mail: lssmd18@gmail.com; Yiguang Bai, Department of Orthopaedics, Nanchong Central Hospital and The Second Clinical Institute of North Sichuan Medical University, 97th South Renmin Road, Shunqing District, Nanchong 637000, Sichuan, China. Tel: +86-0817-2258614; +86-18282050680; E-mail: baiyiguang_sc@163.com

References

[1] Gronchi A, Colombo C, Raut CP. Surgical management of localized soft tissue tumors. Cancer 2014; 120: 2638-2648.

[2] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.

[3] Siegel R, Naishadham D and Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11-30.
[4] Yang VW, Lewis J, Wang TC, Rustgi AK. Colon cancer: an update and future directions. Gastroenterology 2010; 138: 2027-8.
[5] Ottoman RE, Langdon EA, Rochlin DB, Smart CR. Side-Effects of Combined Radiation and Chemotherapy in the Treatment of Malignant Tumors. Radiology 1963; 81: 1014-7.
[6] Palesty JA, Wang W, Javle MM, Yang GY. Side effects of therapy: case 3. Gastric cancer after radiotherapy of pediatric Hodgkin's disease. J Clin Oncol 2004; 22: 2507-9.
[7] Schmeel FC, Schmeel LC, Gast SM, Schmidt-Wolf IG. Adoptive immunotherapy strategies with cytokine-induced killer (CIK) cells in the treatment of hematological malignancies. Int J Mol Sci 2014; 15: 14632-14648.
[8] Pittari G, Filippini P, Gentilcore G, Grivel JC, Rutella S. Revving up natural killer cells and cytokine-induced killer cells against hematological malignancies. Front Immunol 2015; 6: 230.
[9] Hontscha C, Borck Y, Zhou H, Messmer D, Schmidt-Wolf IG. Clinical trials on CIK cells: first report of the international registry on CIK cells (IRCC). J Cancer Res Clin Oncol 2011; 137: 305-10.
[10] 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.
[11] Linn YC and Hui KM. Cytokine-induced killer cells: NK-like T cells with cytotolytic specificity against leukemia. Leuk Lymphoma 2003; 44: 1457-62.
[12] Wu C, Jiang J, Shi L, Xu N. Prospective study of chemotherapy in combination with cytokine-induced killer cells in patients suffering from advanced non-small cell lung cancer. Anticancer Res 2008; 28: 3997-4002.
[13] 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: 250-255.
[14] Gao D, Li C, Xie X, Zhao P, Wei X, Sun W, Liu HC, Alexandrou AT, Jones J, Zhao R, Li JJ. 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.
[15] Jiang JT, Shen YP, Wu CP, Zhu YB, Wei WX, Chen LJ, Zheng X, Sun J, Lu BF, Zhang XG. Increasing the frequency of CIK cells adoptive immunotherapy may decrease risk of death in gastric cancer patients. World J Gastroenterol 2010; 16: 6155-6162.
[16] Jiang J, Xu N, Wu C, Deng H, Lu M, Li M, Xu B, Wu J, Wang R, Xu J, Nilsson-Ehle P. Treatment of advanced gastric cancer by chemotherapy combined with autologous cytokine-induced killer cells. Anticancer Res 2006; 26: 2237-2242.
[17] Liu H, Song J, Yang Z, Zhang X. Effects of cytokine-induced killer cell treatment combined with FOLFOX4 on the recurrence and survival rates for gastric cancer following surgery. Exp Ther Med 2013; 6: 953-956.
[18] Shi L, Zhou Q, Wu J, Ji M, Li G, Jiang J, Wu C. Efficacy of adjuvant immunotherapy with cytokine-induced killer cells in patients with locally advanced gastric cancer. Cancer Immunol Immunother 2012; 61: 2251-9.
[19] Zhao H, Fan Y, Li H, Yu J, Liu L, Cao S, Ren B, Yan F, Ren X. Immunotherapy with Cytokine-Induced Killer Cells as an Adjuvant Treatment for Advanced Gastric Carcinoma: A Retrospective Study of 165 Patients. Cancer Biother Radiopharm 2013; 28: 303-309.
[20] Wang ZX, Cao JX, Liu ZP, Cui YX, Li CY, Li D, Zhang XY, Liu JL, Li JL. Combination of chemotherapy and immunotherapy for colon cancer in China: a meta-analysis. World J Gastroenterol 2014; 20: 1095-106.
[21] Jin C, Li J, Wang Y, Chen X, Che Y, Liu X, Wang X, Sriplung H. Impact of cellular immune function on prognosis of lung cancer patients after cytokine-induced killer cell therapy. Asian Pac J Cancer Prev 2014; 15: 6009-14.
[22] Liu J, Li H, Cao S, Zhang X, Yu J, Qi J, An X, Yu W, Ren X, Hao X. Maintenance therapy with autologous cytokine-induced killer cells in patients with advanced epithelial ovarian cancer after first-line treatment. J Immunother 2014; 37: 115-22.
[23] Pan K, Guan XX, Li YQ, Zhao JJ, Li JJ, Qiu HJ, Weng DS, Wang QJ, Liu Q, Huang LX, He J, Chen SP, Ke ML, Zeng YX, Xia JC. Clinical activity of adjuvant cytokine-induced killer cell immunotherapy in patients with post-mastectomy triple-negative breast cancer. Clin Cancer Res 2014; 20: 3003-11.
[24] Pan K, Li YQ, Wang W, Xu L, Zhang YJ, Zheng HX, Zhao JJ, Qiu HJ, Weng DS, Li JJ, Wang QJ, Huang LX, He J, Chen SP, Ke ML, Wu PH, Chen MS, Li SP, Xia JC, Zeng YX. The efficacy of cytokine-induced killer cell infusion as an adjuvant therapy for postoperative hepatocellular carcinoma patients. Ann Surg Oncol 2013; 20: 4305-11.
[25] 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.
[26] Wu C, Jiang J, Shi L, Xu N. Prospective study of chemotherapy in combination with cytokine-

induced killer cells in patients suffering from advanced non-small cell lung cancer. Anticancer Res 2008; 28: 3997-4002.

[27] Zhao X, Zhang Z, Li H, Huang J, Yang S, Xie T, Huang L, Yue D, Xu L, Wang L, Zhang W, Zhang Y. Cytokine induced killer cell-based immunotherapies in patients with different stages of renal cell carcinoma. Cancer Lett 2015; 362: 192-8.

[28] Zhang J, Zhu L, Zhang Q, He X, Yin Y, Gu Y, Guo R, Lu K, Liu L, Liu P, Shu Y. Effects of cytokine-induced killer cell treatment in colorectal cancer patients: a retrospective study. Biomed Pharmacother 2014; 68: 715-20.

[29] Lee JH, Lee JH, Lim YS, Yeon JE, Song TJ, Yu SJ, Gwak GY, Kim KM, Kim YJ, Lee JW, Yoon JH. Adjuvant Immunotherapy with Autologous Cytokine-induced Killer Cells for Hepatocellular Carcinoma. Gastroenterology 2015; 148: 1383-1391, e6.

[30] Liu J, Li H, Cao S, Zhang X, Yu J, Qi J, An X, Yu W, Ren X, Hao X. Maintenance therapy with autologous cytokine-induced killer cells in patients with advanced epithelial ovarian cancer after first-line treatment. J Immunother 2014; 37: 115-122.

[31] Liu H, Song J, Yang Z, Zhang X. Effects of cytokine-induced killer cell treatment combined with FOLFOX4 on the recurrence and survival rates for gastric cancer following surgery. Exp Ther Med 2013; 6: 953-956.