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REVIEW

Review of Chinese clinical trials on CIK cell treatment for malignancies

Xiao-Dong Li · Bin Xu · Jun Wu · Mei Ji · Bei-Hua Xu · Jing-Ting Jiang · Chang-Ping Wu

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Abstract China is the country where the most clinical trials on CIK cells have been performed. We aimed to provide definite evidence for using CIK cell treatment and extrapolate a common applicative standard for malignancies. We chose the VIP database of Chinese scientific and technological journals to search the literature. We entered the keywords ''CIK'' or ''xi bao yin zi you dao de sha shang xi bao'' (the equivalent Chinese phrase for CIK cells, by Chinese characters) and searched for *in vivo* human trials. In 24 collected trials, 936 patients were treated with CIK cells, 525 men and 246 women. The cultivation time of CIK cells ranged from 7 to 28 days. In five studies, CIK cells were co-cultured with dendritic cells. The total number of CIK cells used ranged from 6×10^6 to 1.5×10^{10}. The total number of DC-CIK cells used ranged from 1×10^9 to 1.3×10^{10}. In all studies, those immune parameters and tumour markers examined increased, but not all increased significantly. Of the reported 563 patients, 40 had a complete response, 126 had a partial response, 125 had a minimal response, 135 had stable disease and 58 had progressive disease. The remaining 76 patients did not reach an objective response. The total response rate was 51.7% (291/563). The toxicities were slight. CIK cell treatment is a promising and safe modality for treating malignancies. We proposed a standard for cultivating CIK cells.

X.-D. Li · J. Wu · M. Ji · B.-H. Xu · C.-P. Wu (✉)
Department of Oncology
Third Affiliated Hospital of Soochow University
185 Juqian Street
Changzhou 213003, People's Republic of China
e-mail: wcpjjt@163.com

B. Xu · J.-T. Jiang (✉)
Department of Tumor Biological Treatment
Third Affiliated Hospital of Soochow University
185 Juqian Street
Changzhou 213003, People's Republic of China
e-mail: jjtnew@163.com

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Introduction

Malignancy is an important cause of human death [1]. It is unfortunate that surgery, chemotherapy, radiotherapy and hyperthermia usually fail to eradicate tumour lesions completely and cause many adverse events [2]. New approaches are urgently needed.

In recent decades, immunotherapy has shown encouraging efficacy and minimal adverse events in cancer therapy [3]. Treatment with cytokine-induced killer (CIK) cells has been investigated as the most promising method over the past twenty years [4].

CIK cells, a subset of T lymphocytes with a natural killer T-cell phenotype expressing both the CD3 and the CD56 markers, present potent non-major histocompatibility complex-restricted cytotoxicity against a variety of tumour target cells in many trials [5–13]. CIK cells have evolved from experimental observations and been used in early clinical studies [12, 14–23]. However, there is no standardised process in the treatment of patients with malignant tumours with CIK cells to date.

Hontsch et al. established an international registry of clinical trials with CIK cells. They collected 11 clinical trials on CIK cells and presented the first report of the registry [2], which is very important and constructive. In that report they mentioned that the increasing number of studies dealing with the treatment of patients with cancer with CIK cells were published only in Chinese, so the results are not well known worldwide [2].

China has the largest population of patients with malignant tumours and China is the country where the most clinical trials on CIK cells have been performed. In our department alone, 2501 patients have received CIK cell treat-

Table 1 Implications and contraindications of the 24 studies

Implications	Contraindications
Expected survival ≥3 months (1 month in 1 study)	Karnofsky score <50
Tumour diagnosis proved by pathologists	Second primary tumours exist
Karnofsky score at least ≥60 (50 in 1 study)	Time interval between chemotherapy or radiotherapy and CIK treatment ≤28 days
No serious disfunction of heart, lung, liver or kidney	Chemotherapy or radiotherapy before or during CIK treatment
Informed consents were obtained	Previous treatment with CIK cells
Leukocyte count $\geq 4\times10^9$ before apheresis	Allergic to anti-allergic drugs or serious electrolyte disturbances
Platelet count at least 100×10^9 before apheresis	Immunosuppressive disease or infectious disease
Aged 4–83 years	Taking immunostimulator steroids within 3 months before CIK cell treatment

ment in the last ten years. It is important to pay attention to the clinical trials on CIK cells.

Methods

Based on these considerations, we collected the data of Chinese clinical trials on CIK cells that focus on the direct efficacy of CIK cell treatment for cancer patients for the first time. We aimed to provide evidence of the success of CIK cell treatment and furthermore extrapolate a common applicative standard for malignancies.

We chose the VIP database of Chinese scientific and technological journals (http://oldweb.cqvip.com), the largest comprehensive literature database in China, to search the literature. We entered the keywords ''CIK'' or ''xi bao yin zi you dao de sha shang xi bao'' (the equivalent Chinese phrase for CIK cells, by Chinese characters) and searched for in vivo human trials, where patients with malignant tumours received CIK cell treatment.

Results

We selected 24 studies that were in accordance with our criteria (Table 1). Expected survival, age and Karnofsky score ≥60 were important inclusion criteria. Meanwhile, Karnofsky score <60, existence of second primary tumours, time interval between chemotherapy or radiotherapy and CIK treatment ≤28 days, chemotherapy or radiotherapy before or during CIK treatment, previous treatment with CIK cells, and immunosuppressive disease or infectious disease were absolute exclusion criteria.

These studies were published in the following medical journals: *Journal of Medical Forum* (1), *Journal of Buthune Military Medical College* (1), *Guangxi Medical Journal* (1), *Journal of Basic and Clinical Oncology* (3), *Hebei Medicine* (1), *Journal of Beijing Medical University* (1), *Journal of Chengdu Medical College* (1), *Science and Technology Review* (1), *Journal of Military Surgeon in Southwest China* (1), *Practical Journal of Cancer* (1), *Journal of Clinical Internal Medicine* (1), *Chinese Journal of Cancer Biotherapy* (1), *Journal of Kunming Medical University* (1), *Chinese Journal of Geriatrics* (1), *Tumor* (1), *Jiangsu Medical Journal* (1), *Chinese Journal of Digestion* (1), *Journal of Fujian Medical University* (1), *Journal of Modern Urology* (1), *Journal of Oncology* (1), *Chinese Journal of Immunology* (1) and *Journal of Qilu Nursing* (1). These trials are published only in Chinese, while the abstracts of most of these articles were presented in both Chinese and English. Those studies published in English and in Chinese journals were excluded. Finally, 24 articles were selected [24–47].

The following data were collected from the 24 articles: name and address of authors, title, journal, volume, issue, page; time range of patients, tumour entity, cell entity (autologous or allogeneic), number of patients (males and females), median- (or average) age and age range, stage of disease, inclusion and exclusion criteria, total number of CIK cells (plus number of CIK cells per infusion and number of infusions), clinical and immunologic responses, values of tumour markers, objective response rate, improvement of quality of life (QoL), follow-up (time period of follow-up, duration of responses) and adverse effects.

After evaluation of each of the 24 trials, we recorded this information and compared results. We put special emphasis on improvement of immune function, objective response rate (ORR), improvement of QoL and outcomes of follow-up.

When the study evaluation was finished, we completed a summary form encompassing the 24 trials, where all information concerning the indices was listed.

Evaluation of patient characteristics

Patients with various malignancies received CIK cell treatment. Of the 24 studies, there were 2 studies for primary hepatocellular carcinoma (HCC), 1 study for HCC after resection, 4 studies for gastric cancer, 1 study for various digestive carcinomas, 1 study for bladder cancer, 4 studies for non-small-cell lung cancer (NSCLC), 1 study for renal cancer, 1 study for various gynaecological carcinomas, 1 study for non-Hodgkin's disease, 4 studies for acute myelogenous leukaemia (AML), 1 study for nasopharyngeal cancer and 3 studies for various malignant tumours.

Table 2 Tumour entity with number of respective patients and gender proportions (total no. of studies=24)

Tumour entity	No. of patients	Male	Female
Primary HCC	97	42	17; 38 unknown
HCC after resection	12	Unknown	Unknown
Pancreatic cancer	4	Unknown	Unknown
Oesophageal cancer	29	Unknown	Unknown
Gastric cancer	231	145	49; 37 unknown
Colorectal cancer	39	Unknown	Unknown
Non-small-cell lung cancer	212	65	21; 126 unknown
Renal cancer	16	5	4; 7 unknown
Bladder cancer	34	27	7
Breast cancer	19	0	19
Endometrium cancer	14	0	14
Ovarian cancer	8	0	8
Cervical cancer	13	0	13
Seminoma	3	3	0
Prostate cancer	3	3	0
Non-Hodgkin lymphoma	12	Unknown	Unknown
Acute myelogenous leukaemia	51	10	4; 37 unknown
Malignant melanoma	9	Unknown	Unknown
Nasopharyngeal cancer	96	70	14; 12 unknown
Cerebroma	4	Unknown	Unknown
Thymoma	2	Unknown	Unknown
Rhabdomyosarcoma	2	Unknown	Unknown
Leiomyosarcoma	2	Unknown	Unknown
Osteosarcoma	2	Unknown	Unknown
Total number	936		

In 24 trials, 936 patients were treated with CIK cells, 525 men and 246 women. The gender of the remaining 165 patients is unknown. The age ranged from 4 to 83 years. In 3 trials of acute leukaemia, there were patients younger than 15 years. In 15 of 24 studies, the median age was given. In 4 of 24 studies, the average age was given. We noticed that gender and age have not been reported as factors related to CIK cell treatment to date, so we included 5 studies that did not report gender and 5 studies that did not report age in our assessment. Tumour entity and gender were shown in the 24 studies in Table 2.

Evaluation of treatment procedure

In 21 of 24 studies, autologous CIK cells were cultivated for treatment. In 1 study, allogeneic CIK cells were cultivated. In 1 study, both autologous and allogeneic CIK cells were cultivated.

Information on cultivation time of CIK cells was available in 21 studies and ranged from 7 to 28 days, but in most ranged from 14 to 21 days.

In 5 studies, CIK cells were co-cultured with dendritic cells (DCs). In these studies, patients received DC-CIK cell treatment. Information on cultivation time of DCs was available in 4 of the 5 studies and ranged from 7 to 12 days. DC-CIK cells were cultivated for 10–14 days, and usually for 12–14 days.

Information on the total number of CIK cells used was available in 16 studies and ranged from 6×10^6 to 1.5×10^{10} in one single course of treatment. The total number of DC-CIK cells used ranged from 1×10^9 to 1.3×10^{10} in one single course of treatment.

CIK cell treatment (including DC-CIK cell treatment) was undertaken every day or every two days and was undertaken for 3–10 days as a single course. The total number of courses was decided by the individual circumstances of patients, such as tolerance to adverse events and discontinuation of treatment.

Evaluation of immunologic response and tumour markers

The immunologic markers examined included the serum levels of CD3, CD4, CD8, CD16, CD19, CD56, CD57, CD3+CD56+, CD3–CD56+ and CD16+56+ T cells, the values of CD3+/CD4+, CD3+/CD8+, CD4+/CD8+, CD3+/CD56+, CD3+/CD16+CD56+ and Th1/Th2, as well as the numbers of B cells and natural killer (NK) cells.

In all studies, all of the immune parameters that had been examined increased, but not all of them increased significantly (Table 3). Overall, we were able to confirm that CIK cell treatment enhances immune function to some extent.

The tumour markers that were examined included the serum levels of AFP, CA-125, CA15-3, CA24-2, CA72-4, CEA, MG-7 Ag and tumour-specific growth factor. In all studies, all of the tumour markers examined decreased, but not all of them decreased significantly (Table 4).

Table 3 Assessment of increasing immune parameters (total no. of studies=24)

Immune parameter	No. of studies where parameter was examined	No. of studies where parameter increased significantly
$CD3^+$ T cells	13	10
$CD4^+$ T cells	13	12
$CD8^+$ T cells	13	9
$CD16^+$ T cells	1	1
$CD19^+$ T cells	3	3
$CD56^+$ T cells	2	2
$CD57^+$ T cells	1	0
$CD3^+CD56^+$	1	1
$CD3^-CD56^+$	1	1
$CD3^+/CD4^+$	1	0
$CD3^+/CD8^+$	1	1
$CD4^+/CD8^+$	7	7
$CD3^+/CD56^+$	2	2
$CD3^+/CD16^+CD56^+$	3	3
Th1/Th2	1	1
B cells	1	0
NK cells	1	1

Table 4 Assessment of decreasing tumour markers (total no. of studies=24)

Tumour marker	No. of studies where marker was examined	No. of studies where marker decreased significantly
AFP	1	1
CA-125	2	1
CA15-3	1	0
CA24-2	1	0
CA72-4	1	1
CEA	3	1
MG-7 Ag	1	1
TSGF	1	1

Evaluation of clinical response and patient outcome

Information on clinical response after CIK cell treatment was available in 14 of the 24 studies. Of the reported 563 patients, 40 had a complete response (CR), 126 had a partial response (PR), 125 had a minimal response (MR), 135 had stable disease (SD), and 58 had progressive disease (PD). The remaining 76 patients did not reach an objective response, but whether they had SD or PD was unknown. The total response rate (RR) was 51.7% (291/563).

Information on patient outcome was available in 10 studies. Four studies reported 1-year overall survival rate (OSR) as 72.5% (74/102), six studies reported 2-year OSR as 66.3% (136/205), one study reported 3-year OSR as 75.5% (40/53) and two studies reported 5-year OSR as 38.2% (42/110).

There was one study on HCC after resection, one on gastric cancer and one on NSCLC. Results showed that (1) in the study on HCC after resection, the median survival times (MSTs) were 18 months for the CIK treatment group and 9 months for the non-CIK treatment group (p=0.049); (2) in the study on gastric cancer, the MSTs were 61 months for the CIK treatment group and 21 months for the non-CIK treatment group (p=0.001); (3) in the study on NSCLC, the MST was 8.5 months for CIK-treated patients, but information on the control group was unknown.

In the study containing 16 renal cancer patients, the average follow-up was 2.3 years (the longest time was 4 years) and no patient developed recurrence and metastasis. In one of four studies on AML, after 16 months' follow-up, 70% of patients remained in continuous complete remission (CCR). In another study on AML, after 3 years' follow-up, 75% of patients remained in CCR and the median time of CCR was 26 months (1–59 months).

Only 1 study on 145 solid tumours reported disease-free survival (DFS). In the 32 patients after resection, 6 had 2-years DFS and 5 had 1-year DFS.

Information on QoL was obtained in 9 of the 24 studies. Overall, patients had improved sleep, increased body weight, less pain and fatigue, and increased appetite. Karnofsky score increased by an average of 10–20 points (Table 5).

Evaluation of adverse effects

Information on adverse effects was available in 14 of the 24 studies. The most common toxicities were low fever,

Table 5 Assessment of improvement of QoL of 9 of the 24 studies

No. of the study	Karnofsky score	Fatigue	Appetite	Apathetic status	Pain	Sleep	Body weight	Short breath
2	74%	95.0%	64.3%	72.0%		95.0%	69.6%	68.9%
4		84%[a]		66%	42%	26%[b]		
7		86%[a]		69%	48%	41%[b]		
10		88.5%	85.7%			91.2%		
13	90.5%							
15	78.1%						84.4%	
21		92.9%[c]		71.4%				
22[d]	62.0%				41.0%		46.0%	
24[e]		$p<0.05$	$p<0.05$			$p<0.05$		

[a]In these two studies, fatigue and appetite were assessed as a whole

[b]In these two studies, weight gain was defined as more than 5% after CIK cell treatment compared to before CIK cell treatment

[c]In this study, fatigue, appetite and apathetic status were assessed whole

[d]In this study, increased Karnofsky score was defined as an increase of more than 20 points after CIK cell treatment, pain relief was defined as more than 50% after CIK cell treatment and weight gain was defined as more than 7% after CIK cell treatment compared to before CIK cell treatment

[e]In this study, fatigue, appetite and sleep were assessed by scoring, and these three indexes were presented as mean±standard deviation

which was usually below 38°C (39°C in 1 study) and subsided spontaneously or within 24 h after anti-inflammatory drugs were administered. Some patients had ague before fever. Other adverse effects included nausea, vomiting, malaise, dizziness, headache, infection in the injection site, conjunctivitis, keratitis, fatigue and rash. These adverse effects were rare and minor.

During the treatment three patients had shock, and one had temporal aphasia and lower limb dysfunction and recovered after symptomatic treatment.

Overall, adverse effects caused by CIK cell treatment were minor in various malignancies. Few patients stopped CIK cell treatment due to adverse effects.

After summarising the 24 clinical trials, we proposed the following standards for cultivating CIK cells.

Separation of blood mononuclear cells and induction of CIK cells

Peripheral blood (50–100 ml) is drawn from patients using heparin as an anticoagulant. Mononuclear cells are isolated by Ficoll-Conray density gradient centrifugation and their viability is assessed by trypan blue exclusion. About 2.0×10^6/ml mononuclear cells are plated onto six-well dishes and cultured with Medium I (containing RPMI 1640 in the presence of human interferon-gamma (IFN-γ, 1.0×10^6 U/l), recombinant human interleukin-2 (IL-2, 5.0×10^5 U/l), 10% inactivated human serum, 25 mM HEPES, 2 mM L-glutamine, penicillin (100 U/ml) and streptomycin (100 μg/ml)). The cells are incubated in a humidified atmosphere with 5% CO_2 at 37°C. After 24 h, monoclonal antibody (MAb) against CD3 (100 μg/l) and IL-1α (1.0×10^5 U/l) are added. After another 48 h, cultures and the supernatant are aspired and the cells are cultured in Medium II (Medium I in the absence of INF-γ). The medium is changed every 3 days.

CIK cell identification and cytotoxic examination

Cells are identified and sorted by flow cytometry on days 1, 7, 14, 21, 28 and 35. In addition, patient's whole blood cells are also separated and sorted by flow cytometry before and after treatments. Cytotoxic activity of CIK cells is determined by co-incubation of CIK cells with various cell lines. Before transfusion, CIK cells are washed twice by 0.9% NaCl and re-suspended in 100 ml 0.9% NaCl containing 1% human albumin. The CIK cells (1.0×10^9 cells) are transfused into the patient within one hour for each biotherapy.

We aimed to observe the direct efficacy of CIK cell treatment to treat malignancies. Other than the 24 trials in our report, few trials were performed within one month after chemotherapy or radiotherapy, so the efficacy of CIK cell treatment could not be evaluated due to the interference of other therapeutic modalities.

CIK cell treatment and other immunotherapy are usually combined with other therapeutic modalities. One important reason is that the definite efficacy of immunotherapy is still not as explicit as that of other therapeutic modalities. After all, prospective, randomised and controlled phase III clinical trials with adequate sample sizes have not been completed. Hence, in an eclectic way, we designed the current study aiming to investigate a relative common standard for CIK cell treatment on malignancies. In some way, the current study can be considered as the preliminary report of the progressive evaluation of the 2501 cases that have been treated with CIK cell treatment in our department. Furthermore, based on our previous work, we were able to propose the standard presented above.

The cases in the present report consist of various stages of malignancies. We consider them an overall reflection of the various circumstances of different malignancies. We could conclude that CIK cell treatment has wide implications, which indicates that it could be used widely. A large

number of cancer patients could benefit from CIK cell treatment without pain due to severe adverse effects.

DC have the strongest function among antigen-presenting cells [48], which mediate immune response via presenting antigens. After DCs are cocultivated with CIK cells, they can promote each other's growth [49]. The synergetic effects have been proven in this report.

In the assessment of survival, we observed a 3-year OSR, even higher than the 1- and 2-years OSRs. The most likely reason is that only one study reported a 3-year OSR and the total sample size was too small.

We did not present the data on times of treatment because results of various studies vary a lot and the differences were huge. Another reason was that information on times of treatment was not adequate. One of the evaluated 24 studies, which was performed by our team, reported that there was a positive correlation between the times of treatment and the risk of death of gastric cancer patients (p=0.0001) [50]. Randomised controlled trials with larger sample sizes or a meta-analysis are needed to draw conclusions regarding these results.

CIK cell treatment is a promising and safe modality for treating malignancies. More clinical trials with large sample sizes are warranted to provide evidence for further application.

Conflict of interest The authors declare that they have no competing or financial interests regarding this paper.

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