

Effect of Chinese Medicine XIAOJI Decoction Combined with Platinum-Based Chemotherapy and Transfusion of Cytokine-Induced Killer Cells in Patients with Stage III B/IV Non-Small Cell Lung Cancer

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Abstract

Objective: The aim of this study was to evaluate the clinical efficacy and safety of cytokine-induced killer (CIK) cells in combination with chemotherapy and Chinese Medicine XIAOJI decoction in patients with advanced NSCLC.

Methods: A total number of 40 patients with advanced NSCLC were randomly assigned into group A (chemotherapy plus XIAOJI decoction) and group B (chemotherapy plus XIAOJI decoction and CIK cell transfusion). Progression free survival (PFS), disease control rate (DCR), overall response rate (ORR), Karnofsky score status (KPS), host cellular immune response and treatment related side effects were assessed.

Results: Our results showed that the PFS in the group B was longer than those in the group A (9.1 months vs. 7.2 months, HR 0.323, 95% CI [0.157, 0.663, P=0.002]. The ORR and the DCR were found no statistical difference between the two groups (20% vs. 10%, P=0.66 and 95% vs. 70%, P=0.10, respectively). The KPS distribution of curative effect in two groups showed significant difference (Z=3.28, P<0.05). The total of uplift ratio was 90% and 80% in the group B and group A, respectively. There was no statistical difference between the total increase rate of the two groups (P>0.05). While the level of CD3+ and CD4+ were significantly higher after treatment in the group B as compared to that in the group A (P=0.04), the level of CD3+ in the control group was lower after treatment (P=0.04) compared to that in the treatment group. There were no immediate adverse reactions in two groups.

Conclusion: This study suggests that CIK cell infusion combined with chemotherapy and XIAOJI decoction improves the survival of patients with advanced NSCLC, which may become more effective therapeutic strategy in patients with advanced lung cancer.

Keywords: Non-small cell lung cancer; Cytokine-induced killer cells; Chinese medicine XIAOJI decoction; Survival; KPS; CD3+/CD4+

Introduction

Lung cancer is one of the most common cancers and as the leading cancer-related morbidity and mortality worldwide [1], NSCLC accounts for 80% of lung cancer. More than two third of NSCLC cases have been diagnosed in the advanced stage, resulting in a poor outcome, with a 5-year survival rate of $\leq 5\%$. The current platinum-based double chemotherapy still remains the standard therapeutic regimen for patients with advanced NSCLC. However, chemotherapy shows limited benefits due to drug resistances and multiple side effects. Therefore, searching and developing a new therapeutic strategy is urgently needed to improve the quality of life and patient survival.

At present, cytokine-induced killer (CIK) cells have been recognized as one of new anti-tumor therapeutic options in broader spectrum of targeted cancer types [2], on the other hand, it reduces recurrence and metastatic rate of malignant tumors, and alleviates adverse effects of conventional chemotherapy [3,4]. Moreover, CIK cells can regulate and enhance immune functions in cancer patients [5], thereby demonstrating the potent to eradicate residual cancer cells and prevent recurrence after chemotherapy. Thus, it provides a basis for clinical practice in combined with chemotherapy in the treatment of advanced tumors including NSCLC.

Traditional Chinese medicine (TCM), which is based on multifactor and comprehensive analysis, and focused on building up healthful vital energy and enhancing resistibility of human beings, shows the

advantage of multiple targets, comprehensive consideration and individualized treatment in the past decades for anti-tumor properties. XIAOJI decoction, an oral liquid of Chinese medicine developed by Dr. WEISHENG-LIU of Guangdong Provincial Hospital of Chinese Medicine in the past several decades, was composed of *Astragalus mongholicus* 30 g, *Coriolus versicolor* 15 g, *Psoralea corylifolia* L. 15 g, *Hedyotis diffusa* 30 g, *Curcuma kwangsiensis* 20 g, Scorpion 10 g, 2 strip Centipedes and Rhubarb 10 g. Previous studies from our groups suggested that XIAOJI decoction improved immunity function, relieved clinical symptoms, and prolonged the survival of cancer patients [6-10]. The *in vitro* and *in vivo* experiments regarding the potential mechanisms of XIAOJI decoction, to some extent, have also been reported previously demonstrating cell growth inhibition and induction of apoptosis of lung cancer cells [11-15].

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Furthermore, transfusion of CIK cells combined with XIAOJI decoction not only had synergistic therapeutic responses in patients with cancer, but also found to have effective biological modification to improve the immune function of patients after chemotherapy. However, studies regarding to the details of the therapeutic roles are limited and the molecular mechanisms of using CIK cells in lung cancer patients still remains to be elucidated. In this study, we explored the potential therapeutic outcome especially the patients using CIK cell infusion combined with chemotherapy and XIAOJI decoction strategy.

Materials and Methods

Patient information

We performed a prospective, randomized controlled single blind study to evaluate the clinical efficacy of CIK cell immunotherapy in patients who were admitted in Department of Oncology of Guangdong Provincial Hospital of Chinese Medicine between March 2011 and March 2014. The patients in accordance with the inclusive criteria were randomized into Group A (control group) and Group B (treatment group) in a ratio of one by one.

The patients have been diagnosed as stage IIIB/IV NSCLC by the pathological examination. Besides, the criteria for patient selection included aged between 18 years and 80 years, A KPS score higher than 60, a measurable lesions and enough bone marrow reserve function were required. The patients have been accepted 4 cycles of platinum chemotherapy. All patients signed an informed consent before enrolling into the study. This study was approved by the Ethics Committees of Guangdong Province Hospital of Chinese Medicine (Approval No. B2014-067-01).

The patients with brain metastasis, hepatic and renal dysfunction, a severe autoimmune disease were excluded. The patients who were using immunosuppressive drugs or long-term use of immunosuppressive drugs after organ transplant were excluded as well. Besides, the criteria for patient exclusion included having severe uncomfortable infection, high fever or active bleeding, and rhesus (RH) negative. Pregnant and lactating women were also excluded. The patients with serious constitution, especially with allergic to IL-2, or HIV positive were also not included. Enrolled patients had no serious cardiovascular disease, diabetes, stubborn or persistent epilepsy. If the patients appeared severe adverse reactions, which were associated with the experimental drugs, should be timely terminated from the trail. Furthermore, in the process of research, patients who withdrew from the study should record the reasons and change the treatment accordingly.

Treatments

All patients in the two groups received XIAOJI decoction (100 ml/ twice/day orally, registered approval number: Guangdong Province Z20080035) and four cycles of chemotherapy with AP regimen (pemetrexed, 500 mg/m², ivd, day1; cisplatin, 75 mg/m², ivd, day1), TP regimen (paclitaxel, 135 mg/m², ivd, day1; cisplatin, 75 mg/m², ivd, day 1), GP regimen (gemcitabine, 1000 mg/m², days 1 and 8; cisplatin, 75 mg/m², ivd, day1), or DP regimen (docetaxel 75 mg/m², ivd, day1; cisplatin, 75 mg/m², ivd, day1). At the same time, the pretreatment of protecting liver or anti-emetic medications were given to the patients. For those treated with CIK cell transfusion, which started 7 days after the period of adjuvant chemotherapy were defined as treatment group. And the others were defined as the control group. Clinical efficacy, Chinese medical syndrome, KPS, host cellular immune response and adverse drug reaction were evaluated and compared in the two groups. The curative effects were evaluated after each treatment.

CIK cell preparation

CIK cells were prepared by the Cell Laboratory of ZMKS International Cancer Therapy Biotechnologies Co., Ltd. (Shenzhen City, Guangdong Province, China) according to previous reports [16,17]. Briefly, the peripheral blood mononuclear cells (PBMCs) were collected using Ficoll density gradient (Tianjin Haoyang Biological Manufacture Co., Ltd, Tianjin, China), rinsed twice by saline solution, and then suspended in AIM-V medium CTS™ (Therapeutic grade, GIBCO, Invitrogen Co., USA). After 4 h of incubation with 5% CO₂ at 37°C, the non-adherent cells were removed by aspiration and the cell density was adjusted to 2 × 10⁶/ml using AIM-V medium containing 1000 U/ml IFN-γ (Shanghai Kelong Biological Manufacture Co., Ltd, Shanghai, China). After 24 h of incubation in the atmosphere with 5% CO₂ at 37°C, 1000 U/ml IL-1 (PeproTech Inc., USA), 1000 U/ml IL-2 (Beijing SL Pharmaceutical CO. LTD., Beijing, China) and 50 ng/ml monoclonal antibody against human CD3 (PeproTech Inc., USA) were added for up to 13 days.

For patients who were accepted CIK transfusion during the period of adjuvant chemotherapy, the CIK cells were infused at the intervals of 7 days after chemotherapy. 3 × 10⁹ CIK cells were transfused into patients within 1 h on days 1-3, which was a total of 9 × 10⁹ cells. This was defined as cycle 1. The subsequent cycle was started at the interval of at least 3 weeks from last transfusion.

Curative effects

The PFS was defined as the interval from the date of randomization to the date of documented disease progression or death for patients. Assessment for clinical response was carried out every two cycles of chemotherapy until disease progression or completion of therapy. The complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were reported according to World Health Organization and International Union against Cancer Criteria. The ORR was the sum of CR and PR, whereas the DCR was the sum of CR, PR and SD. The assessment of QOL was performed according to the lung cancer symptom scale (LCSS), which is a validated patient-rated questionnaire to evaluate the full benefits of treatment for lung cancer. The LCSS includes six important symptoms (appetite, fatigue, cough, dyspnea, hemoptysis and pain) as determined by the patients and the health-care professionals. The changes of KPS and the distribution of T-cell such as CD3⁺, CD4⁺, CD8⁺ and CD4⁺/CD8⁺ were evaluated before and after the treatments.

Statistical Analysis

PASW statistics 18.0 was used to set up a database and statistical analysis. The measurement data were showed as $\bar{x} \pm S$. The homogeneity of variance were analyzed and verified by independent samples t-test within group comparisons, while the comparisons among groups were analyzed by paired simplest-test. The calculation of proportion and ratio of the enumeration data to be compared among groups were analyzed by chi-square test and ranked data was analyzed by rank sum test. The survival analysis was analyzed by Kaplan-Meier test and test level was $\alpha=0.05$.

Results

Patient characteristics

A total of 40 patients were enrolled in this study. The group A and the group B had 20 cases each. The patient information including demographic and clinical characteristics was shown in Table 1. There

were no significant differences in demographic or clinical characteristics between the two groups ($P < 0.05$). The treatment strategies were similar between the two groups except the CIK transfusion.

PFS

All the patients were followed up at the end of 4 cycles of chemotherapy. The PFS curves for the treatment and the control groups are presented in Figure 1 and in Table 2. We found that the PFS in the group B was longer than those in the group A (9.1 months vs. 7.2 months, $P = 0.002$). Moreover, compared to the control group, CIK cell transfusion combined with chemotherapy and XIAOJI decoction showed to prolong the PFS of patients with advanced NSCLC.

ORR and DCR

40 patients selected were successfully completed the treatment. In the treatment group, no one showed CR, 4 cases were PR, 15 cases were SD and 1 case was PD. In the control group, no one was found CR as well, 1 case was PR, 12 cases were SD and 6 cases were PD. The ORR in the treatment and control groups was 20% and 10%, respectively ($P > 0.05$, Table 3). The DCR showed no statistical difference between the two groups (95% vs. 70%, $P > 0.05$, Table 4).

KPS

For the changes of the KPS before and after the treatments, we found that KPS was increased in 11 patients, 7 patients were stable and 2 patients were found a decrease in the treatment group. On the contrary, no patients were observed an increase in KPS, while 16 patients were kept stable and 4 patients were decreased in the control group. The KPS distribution of curative effect in two groups is significant different ($Z = 3.28$, $P < 0.05$, Table 5). The total increase rate in the treatment group was 90%, while 80% was found in the control group (Table 6). There was no statistical difference between the increase rate in the two groups ($P > 0.05$).

T-lymphocytes subset

The T lymphocytes subsets in the two groups were evaluated before and during the adjuvant chemotherapy or immunotherapy (Table 7). While the level of $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ ratios before treatment were no significant difference between the two groups ($P > 0.05$). However, the level of $CD3^+$, $CD4^+$ in the treatment group were significantly elevated after the CIK therapy ($P < 0.05$). In control group, the level of $CD8^+$, $CD4^+/CD8^+$ ratios had no changes ($P < 0.05$). In addition, the level of $CD3^+$ in the control group reduced significantly ($P < 0.05$) after the chemotherapy as compared to that in the treatment group, while the level of $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ ratios in the control group had no significant change ($P < 0.05$). After the treatment, the level of $CD3^+$ in the treatment group were significantly higher than those in the control group ($P < 0.05$).

After the therapy, the $CD3^+$ lymphocytes in treatment group were significantly higher than those in the control group ($t = 3.55$, $P = 0.01$).

Side effects

During chemotherapy, the patients presented the expected side effects, such as temporary fever, headache, chills or anemia, nausea and vomiting. The most common side effects of CIK transfusion were chills, muscular soreness and weak. In this study, only one patient in the treatment group was occurred low fever ($37.8^{\circ}C$) and was relieved by syndrome treatment. To evaluate the safety of the two groups, 20 cases had Grade 1 side effects in the treatment group and 17 cases had Grade 1 side effects (85%), 2 cases of side effect were Grade 2 (10%) and only 1 case was Grade 3 in the control group. In addition, the adverse reactions of the two groups were mild.

Discussion

It has been widely accepted that the dysfunction of immunity system of patients is strongly associated with the occurrence and development of cancer. At the present, the approaches to treat lung cancer are abundant constantly. Adjuvant chemotherapy and targeted

Demographic and clinical features		Treatment group	Control group	χ^2	P value
Sex	Male	13	13	0.00	1.00
	Female	7	7		
Age (years)	<65	14	6	0.00	1.00
	≥ 65	14	6		
Stage	IIIB	5	4	0.14	1.00
	IV	15	16		
KPS	$60 \leq KPS < 80$	8	5	1.03	0.50
	$80 \leq KPS < 100$	12	15		

Table 1: Characteristics of lung cancer patients enrolled: There were no significant differences in demographic or clinical characteristics between the two groups ($P < 0.05$).

Group	Total	PFS (month)		χ^2	P value
		Average PFS ($\bar{x} \pm s$)	Median PFS ($\bar{x} \pm s$)		
Treatment group	20	9.0 ± 0.7	9.1 ± 1.5	4.01	0.002
Control group	20	6.5 ± 0.4	7.2 ± 0.4		

Table 2: The PFS of lung cancer patients in the two groups: The PFS of transfusion of cytokine-induced killer cells combined with chemotherapy and XIAOJI decoction had significantly longer PFS than those treated with chemotherapy plus XIAOJI decoction with no CIK cell therapy (9.1 months vs. 7.2 months, $P = 0.002$).

Group	N	CR+PR	SD+PD	ORR (%)	χ^2	P value
Treatment group	20	4	16	20	0.20	0.66
Control group	20	2	18	10		

Table 3: The ORR of the two groups: The ORR in the treatment and control groups was 20% and 10%, respectively ($P > 0.05$).

Group	N	CR+PR+SD	PD	DCR (%)	χ^2	P value
Treatment group	20	19		95	2.77	0.10
Control group	20	14	6	70		

Table 4: The DCR of the two groups: The DCR showed no statistical difference between the two groups (95% vs. 70%, $P>0.05$).

Group	N	Increase	Stable	Decrease	Z	P value
Treatment group	20	11	7	2	-3.28	0.01
Control group	20	0	16	4		

Table 5: The changes of KPS of patients in the two groups: The KFS distribution of curative effect in two groups is significant different ($Z=3.28$, $P<0.05$).

Group	N	Increase+Stable	The total increase rate (%)	χ^2	P value
Treatment group	20	18	90	0.20	0.66
Control group	20	16	80		

Table 6: The total increase rate distribution of KPS of the two groups: The total increase rate of KPS in the treatment group was 90%, while 80% was found in the control group ($P>0.05$).

Group		CD3 ⁺	CD4 ⁺	CD8 ⁺	CD4 ⁺ /CD8 ⁺
Treatment group	Pre-therapy	59.82 ± 10.31	33.39 ± 7.50	22.39 ± 8.69	1.79 ± 1.23
	Post-therapy	64.09 ± 9.45	36.23 ± 7.26	22.00 ± 8.35	1.89 ± 0.99
	t	-2.75	-2.19	0.25	-0.31
	P value	0.01*	0.04*	0.81	0.76
Control group	Pre-therapy	57.40 ± 13.65	33.61 ± 9.07	19.90 ± 5.78	1.79 ± 0.63
	Post-therapy	52.44 ± 11.25	33.09 ± 12.43	21.46 ± 7.27	1.73 ± 0.83
	t	2.18	0.21	-1.23	0.44
	P value	0.04*	0.84	0.24	0.67

Table 7: T-lymphocytes subset before and during the period of chemotherapy or CIK therapy ($\bar{x} \pm s$): Comparison of the T-cells before and after chemotherapy, *: $P<0.05$.

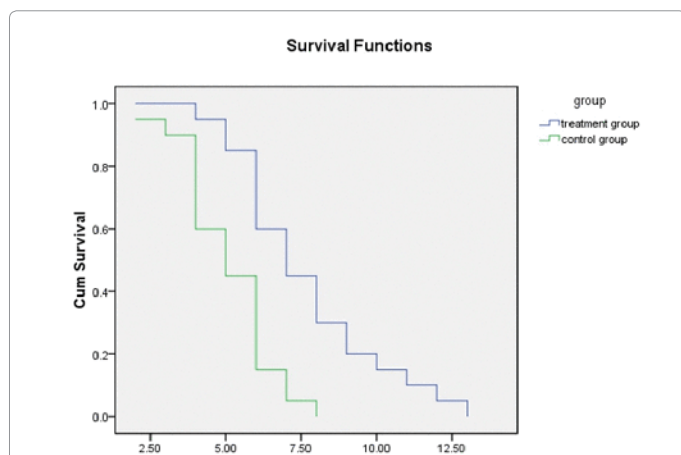


Figure 1: Kaplan-Meier estimates for PFS for patients in the two groups. The PFS of transfusion of cytokine-induced killer cells combined with chemotherapy and XIAOJI decoction. The blue bar represents treatment group which received chemotherapy plus XIAOJI decoction and CIK cell transfusion. The green bar represents control group which received chemotherapy plus XIAOJI decoction. The result showed that significant longer of PFS were achieved in treatment group compared with control group (9.1 months vs. 7.2 months, HR 0.323, 95% CI [0.157, 0.663, $P=0.002$]. This indicated that CIK transfusion prolonged the PFS of patients with advanced stage NSCLC.

therapy are the standard treatment modality for stage IIIB/IV NSCLC. However, immunotherapy has become one of promising strategies for the treatment of certain malignant tumors in recent decades [18], Tumors may release some materials that suppressed the immune system; the immunosuppressive response may be more servers after adjuvant chemotherapy. Thus, the tumors through some mechanisms

to evade destruction by the immune system could be an important reason leading poor outcome in advanced lung cancer. As one of the most important part of complementary alternative medicine (CAM), Chinese medicine XIAOJI decoction was used for treatment of some patients with advanced cancer and found to enhance the immune system [20-22]. Moreover, CIK cells represent the immunotherapy. Thus, evaluating the clinical efficacy of CIK cells combined with platinum chemotherapy and XIAOJI decoction in patients with advanced stage NSCLC can provide a reference for the clinical optimal treatment plan.

Schmidt-Wolf first published an article of CIK cells in 1991 [23]. CIK cells generated by *in vitro* expansion of peripheral blood lymphocytes (PBLs) using anti-CD3 antibodies, IL-2 and IFN- γ . CIK cells consist of three major components: CD3-CD56⁺ CD3⁺CD56⁻ T-cells and 40%~75% of CD3⁺CD56⁺ T-cells. The cytotoxicity mediated by CD3⁺CD56⁺ T cells depends on binding to and formation of cellular conjugation with tumor cells, and production of perforin and granzyme B, two cytolytic factors, but not major histocompatibility complex (MHC) [24]. As we all know, most of the tumor cells do not express MHC or human leukocyte antigen (HLA), which helped tumor cells to escape from the immune system. Thus, CIK cell is a potential utility of non-MHC-based therapy to treat cancers as an immunotherapy. To our knowledge, the truly effect of CIK cells on host immune system still remained unknown. Studies *in vitro* have shown that CIK cells possess cytotoxic activities against a number of tumor cells or freshly isolated tumor samples, including hematopoietic cancer cells and solid tumors. In addition, these CIK cells were demonstrated to possess anti-tumor effect [25]. Thus, the clinical benefit of CIK cells may due to the direct tumor killing activity. In fact, CIK cells are composed of a mixture

of effector and central memory T cells, and the immediate cytotoxic activity was due to the response of T cells. However, the true effects of those central memory T cells are still to be determined. Studies have shown that the CIK cells also produce some cytokines, such as gamma interferon (IFN- γ), tumor necrosis factor α (TNF- α), and express high level of natural-killer group 2, number D (NKG2D), which prone to apoptosis and promote T cell proliferation, this may also be responsible to clinical benefit. Interestingly, CIK cells have also been shown to be effective against multidrug resistance and FasL-positive malignant cells [26]. We believed that CIK cells could kill the residual tumor cells, which resisted the chemotherapy and may be beneficial for the patients with advanced malignancies.

XIAOJI decoction is compound Chinese patent medicine which was developed by Dr. Wei Sheng Liu, in Guangdong province. XIAOJI decoction was composed of *Astragalus mongholicus*, *Coriolus versicolor*, *Psoralea corylifolia* L., *Hedyotis diffusa*, *Curcuma kwangsiensis*, Scorpion, Centipede and Rhubarb. As the monarch drug in a prescription, *Astragalus mongholicus*, *Coriolus versicolor* and *Psoralea corylifolia* can strengthen Spleen and lung Qi, even reinforcing Kidney Qi. While *Hedyotis diffusa*, *Curcuma kwangsiensis*, Scorpion and Centipede are assistant drugs, which can clear away heat toxin, remove the blood stasis. Rhubarb, guide drug, except for cool blood and wipe out cancer toxin, it can dredge meridian as well. Previous studies showed that XIAOJI decoction not only improve immunologic function and clinical symptoms, but also prolong the survival of patients [6-10].

In this study, patients in the treatment group had significant longer PFS than those in the control group ($P=0.002$), this indicated that CIK transfusion prolonged the PFS of patients with advanced stage NSCLC. However, the ORR and DCR showed no statistical difference between the two groups (20% vs. 10%, $P=0.66$ and 95% vs. 70%, $P=0.10$, respectively), the negative result may be resulted from the insufficient cases. Also, our results showed that CIK cells had little effect on reducing tumor size; this could be explained by the fact that the course of the infusion was not enough and the different biological characteristics of the tumor cells might be related. Thus, more numbers of patients and sufficient CIK cell infusion time are required to further determine this.

The KPS distribution of curative effect in two groups is significant different ($Z=3.28$, $P<0.05$) suggesting potential therapeutic benefits in the presence of CIK cell infusion. The possible reason for this may be that the CIK cells could enhance immunity system of human beings resulting in the better physical status. Of note, there was no significant statistical difference between the total increase rate of two groups ($P>0.05$). Thus, more studies are required to further determine this.

The result of CD3⁺, CD4⁺ indicated that the immune status of patients with lung cancer was suppressed and the immune suppression may be more severe after adjuvant chemotherapy. On the other hand, CIK cell infusion can improve the immune function of patients, which was consistent with other studies [27-30], indicating that maintaining and enhancing immune functions played a crucial role in improving quality of life and survival in lung cancer patients. There was only 1 case of mild fever in treatment group after treatment, while the patient could relieve by symptomatic treatment. No significant cardiovascular, hepatic or renal dysfunctions were observed during and after treatment. Nevertheless, more studies are needed to confirm this.

Conclusion

This study shows that CIK cell infusion in combination with chemotherapy and XIAOJI decoction improves the survival and prolongs the PFS of patients with advanced NSCLC. Because of the small sample size, the power of statistical analysis was limited. More studies are required to understand the potential molecular mechanism by these combination treatment strategies.

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