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CYTOKINE INDUCED KILLER CELLS

Efficacy and safety of cord blood–derived cytokine-induced killer cells in treatment of patients with malignancies

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Abstract

Background aims. Adoptive immunotherapy with the use of cytokine-induced killer (CIK) cells represents an effective therapeutic option for treating malignancies. The characteristics and function of cord blood–derived CIK (CB-CIK) cells have been evaluated both *in vitro* and *in vivo*. In this study, we assessed the efficacy and safety of administering CB-CIK cells to patients with cancer. *Methods.* In this retrospective clinical trial, 15 patients with cancer received CB-CIK therapy with different cycles from April 2012 to August 2014. CB-CIK cells demonstrated a high percentage of main functional fraction $CD3^+CD56^+$ and efficient anti-tumor activity *in vitro*. *Results.* After the infusion of CB-CIK cells, the subsets of $CD3^+CD4^+$ T lymphocytes and $CD3^-CD56^+$ T cells in the peripheral blood were significantly increased compared with those before the therapy. Of 15 patients, one patient with hepatocellular cancer and one patient with esophageal cancer achieved complete responses, two patients with ovarian cancer obtained partial remissions, 10 patients had stable disease and one patient with hepatocellular cancer had progressive disease. Acute toxicities including fever, slight fever, dizziness and other neurologic toxicities were few and occurred in patients after infusion of CB-CIK cells. *Conclusions.* These results demonstrated the feasibility and safety of treating malignancies with CB-CIK cells. The study provides a potential therapeutic approach for the patients with poor health or older patients who cannot tolerate repeated collection of blood.

Key Words: *cord blood, cytokine-induced killer cells, efficacy, malignancies, safety*

Introduction

Immunotherapy has recently become the fourth most important treatment modality for cancer, ranked after surgery, chemotherapy and radiotherapy [1,2]. It is a promising treatment option for tumors. Various types of immune cells have been used in clinical trials, including lymphokine-activated killer (LAK) cells, tumor-infiltrating lymphocytes (TILs) and cytokine-induced killer (CIK) cells. LAK cells demonstrated potent *in vitro* cytotoxicity against tumor cells and led to the regression of established tumors in animal models [3,4]. In clinical studies, LAK cells had demonstrated modest efficacy against metastatic cancer such as renal cell carcinoma and melanoma [5]. Many patients with cancer were ineligible for TIL-based therapy because their TILs did not expand sufficiently. Meanwhile, their tumors had lost expression of antigens or major histocompatibility complex molecules or had extremely low numbers of TILs [6,7]. CIK cells have been recognized as another type of anti-tumor cells, which can be readily amplified from bone marrow, peripheral blood (PB) and more recently from cord blood (CB) in the presence of anti-CD3 monoclonal antibody (mAb), interferon

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Table I. Patient clinical characteristics.

Patient No.	Age (years)	Sex	Weight (kg)	Tumor	Stage	Histologic differentiation
1	33	Male	84	Colon cancer	III B	Poor differentiation
2	38	Male	75	Colon cancer	IV	Moderate differentiation
3	41	Female	49	Colon cancer	IV	Moderate differentiation
4	51	Male	55	Colon cancer	IV	Poor differentiation
5	61	Female	54	Rectal cancer	IV	Moderate differentiation
6	58	Female	51	Ovarian cancer	IV	Poor differentiation
7	49	Female	56	Ovarian cancer	IV	Poor differentiation
8	57	Female	60	Ovarian cancer	IV	Poor differentiation
9	63	Female	65	Ovarian cancer	IV	Poor differentiation
10	34	Female	49	Hepatocellular cancer	IIIA	Poor differentiation
11	48	Female	60	Hepatocellular cancer	IIIA	Moderate differentiation
12	54	Female	53	Gastric cancer	IV	Poor differentiation
13	62	Female	56	Pancreatic cancer	IV	Poor differentiation
14	62	Male	60	Lung cancer	IV	Moderate differentiation
15	54	Female	65	Esophagus cancer	II A	Poor differentiation

(IFN)-γ and interleukin (IL)-2 [8,9]. CIK cells are a subset of natural killer T lymphocytes (NKT) that are responsible for their cytotoxicity, and this subpopulation is derived from $CD3^+CD56^-$ T cells that acquire the CD56 marker [10,11]. Compared with LAK cells, CIK cells exhibit enhanced lytic activity against tumor cells, higher proliferation rate and relatively lower toxicity. Furthermore, CIK cells can regulate and generally enhance the immune functions in patients with cancer [12,13].

The cord blood–derived CIK (CB-CIK) cells can be easily and largely expanded *in vitro* [14,15]. It has also been shown that CB-CIK cells can kill a variety of tumors, and the cytotoxic activity against tumor cells is associated with the $CD3^+CD56^+$ cell subpopulation [16]. We had reported the phenotypic characterization and anti-tumor effects of CB-CIK cells [17]. Compared with the peripheral blood–derived CIK (PB-CIK) cells, CB-CIK cells had increased proliferation rates, low immunogenicity and higher percentage of main functional fraction $CD3^+CD56^+$ and exhibited more potent anti-tumor efficacy against various malignancies. These results demonstrated that CB-CIK cells could be more effective for treatment of patients with cancer. The anti-apoptosis activity of CB-CIK cells after treatment with cisplatin was higher, which indicates that CB-CIK cells might have a long survival period *in vivo* when combined with chemotherapy. In animal studies, the CB-CIK cells not only can prevent tumor growth but also improve host immune function. Furthermore, the cytotoxic effect of CB-CIK cells can be enhanced by human IFN-α, sunitinib or some adjunvants such as *Pseudomonas aeruginosa* injection (PA-MSHA) [18–20]. The biological characteristics and function analysis of CB-CIK cells suggest a potential clinical application against cancer.

CIK cells have been evaluated as an immunotherapy for patients with advanced solid malignancy such as lung cancer, ovarian cancer and colorectal cancer [21,22]. Nevertheless, there are few reports about the clinical application of CB-CIK cells. In this study, the efficacy and safety of CB-CIK cells were observed in patients with various malignancies.

Table II. Treatment protocols and Karnofsky Performance Status score of patients.

Patient No.	Surgery	Chemotherapy	Karnofsky performance status
1	Yes	Etoposide + cisplatin	90
2	Yes	Folfox6	90
3	No	Irinotecan +fluorouracil	80
4	Yes	Docetaxel + S-1	85
5	Yes	Irinotecan +fluorouracil	85
6	Yes	PT[a]	80
7	Yes	PT[a]	95
8	Yes	PT[a]	95
9	Yes	PT	80
10	Yes	No	65
11	Yes	No	95
12	Yes	Oxaliplatin+ S-1	85
13	Yes	Gemcitabine	80
14	No	Docetaxel +oxaliplatin	75
15	Yes	No	95

[a]Ciaplatin plus paclitaxel.

Methods

Patients

We conducted the retrospective study with patients who were admitted in the First Affiliated Hospital of Zhengzhou University from April 2012 to August 2014. All the patients with histologically documented malignancies were enrolled in the protocol, and written informed consent was provided in accordance with the *Declaration of Helsinki*. Enrolling criteria for patients included survival duration of more than 3 months, Karnofsky Performance Status more than