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REVIEW

Cytokine induced killer cell immunotherapy in cancer treatment: from bench to bedside

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Abstract— Cytokine-induced killer (CIK) cells are T effector cells generated by monocytes cultured and stimulated by cytokines. CIK cells were studied for more than 20 years ago. They can cause lysis of tumor cells that of both autologous and allogeneic origins, so that they were used in cancer treatment. This review aimed to summarize advancements of CIK cells and their current clinical applications in cancer treatment. In general, CIK cells were widely clinically used for recent 5 years. They gave promising results in hepatocellular carcinoma, lung cancer, breast cancer, renal cancer, and treatment. Looking into the future, CIK cell based immunotherapy will become an important tool in cancer treatment.

Keywords— Adoptive cell therapy; Cytokine induced killer cells; Cancer treatment; Immunotherapy; Cell therapy.

INTRODUCTION

Adoptive cell therapy of cancer demonstrated in mice more than 50 years ago (Mitchison, 1955). During 50 years, some adoptive cell therapies were developed with many bright results in both pre-clinic and clinic. To date, more than 10.000 patients with cancer were treated by adoptive cell therapies. Most of them used CIK cell therapy and dendritic cell (DC) therapy. Different to DCs that cause tumor antigen-specific immune responses, CIK cell therapy can create non-antigen specific immune responses. CIK cells possess non-MHC-restricted cytolytic activities against to cancer cells. From some particular mechanisms of cancer cell recognition, CIK cells can detect and attack cancer cells. This review summarizes some characteristics of CIK cells and an update of clinical applications of CIK cells in cancer treatment.

CIK CELL PHENOTYPES

CIK cells are a heterogeneous population of T lymphocytes with NK phenotypes and functional properties. This cell population was named "cytokine induced killer" cells because they were generated under effects of cytokines. These CIK cells can cause toxic malignant cells followed the manner of MHC-unrestricted cytotoxicity. CIK cells were produced by incubation of peripheral blood monocytes in medium plus with INF-gamma, mAb anti-CD3 and IL-2 (Schmidt-Wolf et al., 1991). After 2-3 weeks of culture, CIK cells are expanded in vitro from few to more than 1000 fold (Marin et al., 2006; Pals et al., 2007; Thorne et al., 2006).

As heterogeneous population, CIK cells contain at least 3 cell sub-populations included $CD3^+CD56^+$, $CD3^+CD56^-$, $CD3^-CD56^+$ with largest population $CD3^+CD56^+$. Some studies determined anti-tumor activity in CIK cells belongs to fraction $CD3^+CD56^+$ (Edinger et al., 2003; Pals et al., 2007). In fact, in the human body, this population always exists with phenotype of lymphocytes accounting from 1-5% of T cells (Maccalli et al., 2007). With this phenotype, CIK cells hold both lymphocytes and natural killer cells activities.

In vitro, CIK cells easily were produced by culture of peripheral blood mononuclear cells in medium plus with INF-gamma on day 0, and anti-CD3 OKT3 (50 ng/ml) and IL-2 (500 IU/mL) on the next day, followed by the addition of IL-2 during the culture. INF-gamma was used to increase the cytotoxicity of CIK cells, while anti-CD3 acted as a mitogenic agent on T cells. The cocktail with INF-gamma, anti-CD3

and IL-2 holds an important role that triggers the T cell expansion and increases the T cell cytotoxicity. So that by the *in vitro* cell culture, CIK cells were expanded with a large amount and high activity of T cells and NK cells. Some studies showed that CIK cells produced IL-2, IL-7 and IL-12. So that to produce CIK cells, besides IL-2 addition, some authors used IL-7 and IL-12 also could produce high anti-tumor activity CIK cells (Farag et al., 2002; Huang et al., 2006). To date, almost studies used CIK cells were induced from peripheral blood, but CIK cells also can be produced from bone marrow and cord blood (Alvarnas et al., 2001; Introna et al., 2006).

MECHANISM OF ANTI-TUMOR ACTIVITY

The mechanism of anti-tumor activity of CIK cells has not completely clarified. However, some pathways related to this activity were identified. It is showed that CIK cells significantly inhibited the anti-tumor activity when they were blocked lymphocyte function associated antigen -1 (LFA-1) and cell adhesion molecule -1 (ICAM-1) (Schmidt-Wolf et al., 1996; Schmidt-Wolf et al., 1993). In fact, CIK cells were treated with dibutyryl (db)-cAMP that prevents the conversion of LFA-11 into a high affinity receptor for ICAM-1, were inhibited to release perforin and granzyme (Mehta et al., 1995).

Another mechanism also was detected about tumor recognition of CIK cells that similar in NK cells. CIK cells recognize the tumor antigen via NKG2D. NKG2D (Natural killer group 2 member D) is one member of the c-type lectin-activating receptor family. NKG2D is expressed on all NK cells. Ligands for NKG2D were restrictedly expressed in malignant cells (Diefenbach et al., 2000; Jamieson et al., 2002). When induced with IFN-gamma, IL-2 and anti-CD3, NKG2D was highly expressed in CIK cells. Interaction between NKG2D and tumor antigen that expressed in tumor cells will cause the cytolytic effect by perforin and granzyme release of CIK cells.

Besides the recognition of CIK cells by NKG2D, CIK cells also specifically attack tumor cells by another mechanism. Recent studies showed that co-culture of CIK cells and induced DCs that can present tumor antigen can enhance the CIK cells to attack tumor cells (Marten et al., 2001; Nagaraj et al., 2004; Ziske et al., 2001).

CLINICAL TRIALS

CIK cells were used in clinical trials for some diseases (**Table 1, 2**). Particularly, CIK cell therapy in combination with some conventional therapies or dendritic cells was studied in Phase III of lung cancer, in Phase IV of hepatocellular carcinoma. Moreover, CIK cell therapy also used in clinical trials for other cancers such as ovarian cancer, colorectal cancer, renal cancer, leukemia, breast cancer…

In HCC, to increase the efficacy of trans-catheter arterial chemoembolization (TACE) on HCC treatment, Hao et al. (2010) combined TACE and CIK cells. The results showed that the efficacy of TACE was significantly improved. Wang et al. (2013) showed that the disease control rate was 67.7% in patients transfused with CIK cells (Wang et al., 2013). Similarly, in HCC patients, Huang et al. (2013) showed that CIK cell immunotherapy was valuable therapeutic strategy to prevent recurrence and metastasis in HCC patients after TACE and RFA (Huang et al., 2013). Effects of CIK cell transfusion caused a significant increased of CD3+, CD4+, CD4+CD8+ and CD3+CD4+ T cells (Ma et al., 2012), improved the immunological status in HCC patients (Shi et al., 2004), reduce the level of serum AFP and anti-HBV and decrease the 1-year recurrence rate of patients with HCC after curative TACE plus RFA (Pan et al., 2010).

CIK cells represent a promising immunotherapy for the treatment of gastrointestinal tumors (Jakel et al., 2014). Adjuvant transfusion of CIK cells prolongs DFS in patients with colorectal cancer from 29.35 ± 6.39 % in control without CIK cells to 59.65 ± 24.80 % with CIK transfusion, and no immediate adverse reactions to the CIK cell transfusions (Zhu et al., 2013). DC/CIK therapy also reduced the risk of post-operative disease progression with an increased OS in gastric and colorectal cancer patients (Gao et al., 2014).

Table 1. Clinical trials in the world

Region Name	Number of Studies
East Asia	32
Europe	1
North America	5
Southeast Asia	4
World	**43**

DC-CIK cell therapy markedly prolongs survival time enhances immune function and improves the efficacy of the treatment of breast cancer patients. In treated patients, the percentage of T cells ($CD3^+$, $CD4^+$ and $CD4^+CD8^+$), $CD16^+$ monocytes, and $CD3^+CD56^+$ natural killer T cells, the levels of interleukin-2, interleukin-12, tumor necrosis factor-α, interferon-γ, and nucleolar organizer region protein in the peripheral blood of cancer patients was significantly increased (Wang et al., 2014b). DC-CIK was feasible and effective in treating advanced renal cancer (Kim et al., 2014; Su et al., 2010). Wang et al. showed an objective response rate (ORR) of 39% and a disease control rate (DCR) of as 75%. No clinically significant side effects were observed (Wang et al., 2014a). In another study, Zhan et al. combined CIK cells with DCs and showed that TL-pulsed DC-CIK cells could prevent recurrence/metastasis and increase the overall survival rate after surgery in localized or locally advanced renal carcino-

ma with the overall survival rates significantly higher in the DC-CIK group and IFN-α group than that in the control group (Zhan et al., 2012).

CIK cells also were successfully used in ovarian cancer treatment. Liu at al. (2014) transfused CIK cells in a clinical with 94 patients with IIB-IV grade ovarian cancer. They showed that a median PFS were 37.7 months in the treatment group and 22.2 months in the control group. After 2 courses of CIK cells transfusion, the proportion of CD4CD25CD127 regular T cells in the peripheral blood significantly decreased (Liu et al., 2014).

In lung cancer, CIK cells have important effects on antitumor in both early-stage disease (I-IIIA) (Li et al., 2012) and advanced stage disease (IIIB-V) (Li et al., 2012; Shi et al., 2012; Zhong et al., 2011). By the research with 87 paired patients, Li et al. (2012) suggested that CIK cell immunotherapy could improve the efficacy of conventional chemotherapy in NSCLC patients, and increased frequency of CIK cell treatment could further enhance the beneficial effects. Yang et al. (2013) also confirmed that CIK cells plus DC could increased the 1- and 2-year overall survival rates up to 57.2 compared to 27.0 % in control (Yang et al., 2013).

Recent studies used CIK cells to target cancer stem cells (CSCs). Gammaitoni et al (2013) demonstrated that CIK tumor killing activity against melanoma CSCs was intense and comparable with results reported against differentiated metastatic melanoma cells. CIK cell transplantation resulted in delayed tumor growth, increased necrotic areas, and lymphocyte infiltration at tumor sites (Gammaitoni et al., 2013).

Conclusion

Immune therapies are promising therapies for cancer treatment. CIK cells hold high anti-tumor activity in MHC unrestricted manner. These cells are easily produced with a large amount from peripheral blood by cultured peripheral blood mononuclear cells with INF-gamma, IL-2 and anti-CD3. CIK cells have used to treat several cancers with good results. Especially, CIK cells based therapy clinically studied in phase IV in hepatocellular carcinoma, and phase III in lung cancer. From these results, it hopes that CIK cell therapy rapidly pushes into routine application in lung cancer or hepatocellular carcinoma in the near future.

Table 2. Clinical trials with CIK cell therapy in cancer treatment

Registered number	Titles	Phase	Intervention
NCT01828008	Treatment of CD20 Antibody Plus CIK for Patients With Refractory Lymphomas	I/II	
NCT01783951	Study of S-1 Plus DC-CIK for Patients With Advanced Gastric Cancer	I/II	Mononuclear cells were collected aseptically with blood cell separator composition aphaeresis 3 days before administrating S-1 , and cultured DC-CIK cells for 10 days. Cells were infused back to the patients in 3 times.
NCT01781520	Study of S-1 Plus DC-CIK for Patients With Unresectable Locally Advanced Pancreatic Cancer	I/II	Mononuclear cells were collected aseptically with blood cell separator composition aphaeresis 3 days before administrating S-1, and cultured DC-CIK cells for 10 days. Cells were infused back to the patients in 3 times.
NCT01906632	Gene Expression Profiling of Malignant Tumor Predict the Therapeutic Response of DC-CIK Immunotherapy	I/II	The patients with malignant tumor are treated with dendritic cells (DC) plus cytokine induced killer cells (CIK)
NCT01758679	A Clinical Trail of Iodine[131I] Metuximab Injection With CIK Cells for Preventing Hepatocellular Carcinoma	IV	The present clinical trial is intended to examine the efficacy and safety of radioimmunotherapy via intravenous infusion of licartin plus sequential immunotherapy of CIK cell in the controls of disease progression, effective prolonging of recurrent time and prevention of recurrence or metastasis of primary hepatocellular carcinoma.
NCT01898793	Cytokine-induced Memory-like NK Cells in Patients With Relapsed and Refractory AML	I	Patients under-go CIML NK cell infusion over 15-60 minutes on day 0. Interleukin-2: Patients receive aldesleukin SC every other day for 2 weeks starting on day 1 (total of 7 doses)
NCT01186809	Cytokine Induced Killer (CIK) Cells In Leukemia Patients (CIK2)	II	In vitro expanded CIK cells

Table 2. Clinical trials with CIK cell therapy in cancer treatment (*continued)*

Registered number	Titles	Phase	Intervention
NCT01655628	Metastatic Nasopharyngeal Carcinoma	II	Patients will maintain autologous CIK cells for 8 cycles (every 4 weeks).
NCT00185757	Cytokine Induced Killer Cells as Post-Transplant Immunotherapy Following Allogeneic Hematopoietic Cell Transplantation	I	The initial dose utilized will be $1x10^7$ expanded cells/kg. The dose will be increased to $5x10^7$ expanded cells/kg and $1x10^8$ expanded cells/kg in successive escalations based on no significant infusional toxicity or GVHD in the recipients
NCT01868490	The Adoptive Immunotherapy for Solid Tumors Using Modified Autologous Cytokine-induced Killer Cells	I/II	CIK cells at least 10^9 CIK cells, IV on day 0, 14, 28
NCT01929499	Efficacy of Adjuvant Cytokine-induced Killer Cells in Colon Cancer (CIKCC)	II	After colectomy, patients will accept adjuvant chemotherapy for 6 months, that is 6-8 cycles of CapeOX regimens, or 10-12 cycles of mFolfox6 regiments, followed by 6-8 cycles of cytokine-induced killer cells (CIK) therapy at least 2 weeks later.
NCT00815321	Autologous Cytokine Induced Killer Cells (CIK) for Chronic Myeloid Leukemia (CML) Patients on Standard Drug Therapy	II	CIK cells will be infused into patients at regular 3-weekly intervals for 4 infusions. The target cell dose per infusion is10^{10} CD3 cells.
NCT01914263	Safety Study of Cord Blood-derived Cytokine-induced Killer Cells in Patients With Solid Tumor After Radical Resection	I	The eligible patients are infused a single dose of $8x10^9$ CIK cells.
NCT01392989	Post T-plant Infusion of Allogeneic Cytokine Induced Killer Cells as Consolidative Therapy in Myelodysplastic Syndromes/Myeloproliferative Disorders	II	Target dose of $\geq 5 \times 10^6$ $CD34^+$ cells/kg of recipient body weight plus an additional 2.10^9 mononuclear cells.
NCT00394381	Autologous Cytokine-induced Killer Cell Adoptive Immunotherapy for Acute Myeloid Leukemia and Myelodysplastic Syndrome	I/II	Autologous CIK cells will be infused at timed intervals after autologous transplant for AML for group 1 patients, and with or without some cytoreduction treatment for group 2 patients
NCT01902875	Preconditioning Chemotherapy Combination With Cytokine Induced Killer Cell (CIK) Immunotherapy	I/II	Peripheral blood mononuclear cell are separated before chemotherapy, and before each CIK cell transfusion. CIK cells are transfused on D7, D14, D21 (with simultaneous transfusion of IL-2 2 million units).
NCT01592422	Maintenance Therapy With Autologous Cytokine-induced Killer Cells for Small Cell Lung Cancer	II	Subjects receive autologous CIK cell infusion every month in the absence of disease progression or unacceptable toxicity.
NCT01481259	Maintenance Therapy With Autologous Cytokine-induced Killer Cells for Nonsquamous Non-small Cell Lung Cancer	II/III	Subjects receive autologous cytokine-induced killer cell infusion every 21 days in the absence of disease progression or unacceptable toxicity.
NCT01871480	CIK Cell Transfusion Plus Gefitinib As Second Or Third-Line Treatment for Advanced Adenocarcinoma Non-Small Cell Lung Cancer	II	CIK cells: intravenous infusions; D14-16; one cycle every month, at least 6 cycles; Gefitinib treated with 250mg for daily oral administration in the absence of disease progression or unacceptable toxicity.
NCT00460694	Allogeneic Cytokine-induced Killer Immunotherapy for Relapse After Allogeneic Marrow Transplant for Haematological Malignancies (alloCIK)	I/II	Infusion of allogeneic CIK cells
NCT01631357	Study of Chemotherapy Combination With Autologous Cytokine-Induced Killer Cell Immunotherapy to Treat Lung Cancer (CIK)	II/III	Cytokine-induced killer cell + cisplatin + paclitaxel. CIK cells: intravenous infusions; $5\text{-}6 \times 10^9$ CIK cells, days 14 and 15; one cycle every month; at least 6 cycles.
NCT00769106	Study of Cytokine-induced Killer Cell (CIK) Treatment in Patients After Resection of Liver Cancer (HCC-CIK)	III	CIK cell treatment every two weeks, for 4 cycles

Table 2. Clinical trials with CIK cell therapy in cancer treatment (*continued)*

Registered number	Titles	Phase	Intervention
NCT01924156	DC Vaccine Combined With CIK Cells in Patients With Renal Cell Carcinoma	I/II	Adenovirus-transfected autologous DC + CIK cells
NCT01240005	Cytokine Induced Killer Cells Stimulated by DC Immunotherapy for Renal Cell Carcinoma	I/II	Renal cell carcinoma patients were treated with three intravenous infusions of DC activated CIK cells at 1-day intervals.
NCT01898663	DCs Vaccine Combined With Cytokine-induced Killer Cells in Patients With High-risk Soft Tissue Sarcoma	I/II	Adenovirus-transfected autologous DCs + CIK cells
NCT01821495	Study of DC-CIK to Treat NPC	II	Dendritic and Cytokine-induced Killer Cells
NCT00862303	DC Vaccine Therapy Combined With Cytokine-Induced Killer Cell in Treating Patients With Renal Cell Carcinoma	I/II	Patients receive autologous dendritic cells (DC) loaded with autologous tumor lysates (DC vaccine) by endemic injection and infusion of CIK cells.
NCT01894373	Autologous Cytokine Induced Killer Cells (CIK) for Patients With Severe Psoriasis	I/II	Induced Killer (CIK) cells Procedure: Infusion of autologous CIK cells
NCT01235845	Dendritic Cell (DC) Activated Cytokine-induced Killer Cell (DCIK) Combined With DC Treatment for Glioma	I/II	Dendritic cells pulsed With tumor lysates were injected back into the patient intradermally close to a lymph node, DC vaccinations will be given every week for a total of four vaccinations.
NCT00477035	Post-transplant Autologous Cytokine-induced Killer (CIK) Cells for Treatment of High Risk Hematologic Malignancies	I/II	
NCT01821482	A Study of DC-CIK to Treat Hepatocellular Carcinoma	II	After complete resection or TACE, patients will receive 3 cycles of DC-CIK (every 4 weeks)
NCT01839539	Study of DC-CIK to Treat Colorectal Cancer	II	After neoadjuvant and (or) adjuvant chemotherapy or (and) radiotherapy according to NCCN guidelines, patients will receive 2-3 cycles of DC-CIK treatment (every 4 weeks).
NCT01498055	Autologous CIK Cells Infusion for the Treatment of Lung Cancer: a Randomized Controlled Study	II/III	
NCT01749865	CIK Treatment for HCC Patient Underwent Radical Resection	III	CIK Cells treatment for 4 cycles
NCT01395056	Study of Chemotherapy With Adoptive Cellular Therapy With DC-CIK Cells in Triple Negative Breast Cancer Patients (DCCIK)	I/II	All the patients enrolled will be given standard cyclophosphamide combined thiotepa and carboplatin chemotherapy and cellular therapy.Cellular therapy consisting of one cycle of chemotherapy followed by an apheresis and ex vivo cultures to generate DC and CIK, followed by low-dose Oral Cyclophosphamide
NCT01956630	Clinical Study of DC Plus CIK for Patients With Relapse Acute Leukemia After Allo-HSCT	I/II	Patients received four subcutaneous injections of 2-5×10^7 cells of DCs at the groin, axilla, and neck respectively on days 7, 9, 11, and 13 and i.v. infusions of 2-15×10e9 CIK on days 11 and 13 per cycle.
NCT01691625	Concurrent Chemoradiation With or Without DC-CIK Immunotherapy in Treating Locally Advanced Esophageal Cancer	I/II	Mononuclear cells were collected aseptically with blood cell separator composition apheresis 3 days before concurrent chemoradiation, and cultured DC-CIK cells for 10 days. Cells were infused back to the patients in 3 times between the Chemoradiation intermittent period.

ABBREVIATIONS

CIK: Cytokine-induced killer; DC: Dendritic cell; HCC: Hepatocellular carcinoma; ICAM-1: Cell adhesion molecule -1; LFA-1: Lymphocyte function associated antigen-1; MHC: Major histocompatibility complex; NK: Natural killer cells; NKG2D: Natural killer group 2 member D; TACE: Transcatheter arterial chemoembolization

Competing interests

The authors declare that they have no competing interests.

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