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Journal of Immunology & Clinical Research

Review Article

Prospects in Adoptive Cell Transfer Therapy for Cancer

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Submitted: 13 July 2013

Accepted: 08 August 2013

Published: 14 August 2013

Keywords

- Adoptive cell transfer therapy (ACT)
- Lymphokine-activated killer (LAK) cells
- Cytokine-induced killer (CIK) cells
- Tumor-infiltrating lymphocytes (TIL)
- Genetically-engineered T lymphocytes

Abstract

Cancer treatment still is a challenge task for both basic scientists and clinicians. Conventional treatments for cancer such as surgery, radiation and chemotherapy seem inadequate. Recent developments in immunotherapy make it a more promising method for cancer treatment. Clinical trials have demonstrated that adoptive cell transfer therapy using anti-tumor tumor-infiltrating lymphocytes is very effective in the treatment of patients with metastatic melanoma. Genetically-engineered T lymphocytes with anti-tumor activities may also be used effectively in adoptive cell transfer therapy for cancer. It is, therefore, desirable to establish a bank of anti-tumor tumor-infiltrating lymphocytes and/or genetically-engineered anti-tumor T lymphocytes, which are active against all known tumor antigens. This program may provide an effective adoptive cell transfer therapy for cancer patients in the future as long as specific tumor antigens are identified.

INTRODUCTION

It has been documented that immunosurveillance plays an important role in cancer development in both human and animals [1,2]. Cancer immunosurveillance is the function of immune system in recognizing and reacting against aberrant cancer cells in the body. Thus, the interactions between cancer cells and immune cells play a pivotal role in cancer development. In cancer patients, however, tumors grow, suggesting that anti-tumor immune responses are either not sufficiently vigorous to eliminate cancer cells or the anti-tumor immunity is suppressed.

Recent clinical trials have demonstrated that adoptive cell transfer therapy (ACT) with anti-tumor lymphocytes can cause cancer regression in approximately 70% of patients with metastatic melanoma [3,4]. Therefore, *in vitro* manipulation of anti-tumor immunity may be used in the effective treatment of cancer patients. In this review, the development and prospects of ACT for cancer are discussed. Cancer immunotherapy has been noted as one of six Areas to Watch in 2013 [5], and it is expected that ACT with anti-tumor lymphocytes will be extensively used in cancer treatment in the near future.

LYMPHOKINE-ACTIVATED KILLER (LAK) CELLS

LAK cells are the activated peripheral blood mononuclear cells (PBMC) from cancer patient and normal donors after *in vitro* stimulation by interleukin-2 (IL-2) for 4-6 days [6]. They are derived from natural killer (NK) and T cells in PBMC. LAK cells have anti-tumor activity *in vitro* against various cancer cells. In 1984, it was demonstrated that LAK cells in combination with IL-2 were very effective in eradicating tumors in mice with established pulmonary sarcoma metastases [7]. In 1985, Rosenberg *et al.* used LAK cells for ACT in clinical trials for patients with metastatic cancer [8]. After ACT with LAK cells, the reduction of tumor burdens was achieved in approximately 50% of the 25 treated patients and one patient had a complete tumor regression [8]. However, the response in cancer patients was sustained only for a short period of time [9]. The anti-tumor activity of LAK cells is maintained by IL-2, and thus high-dose of IL-2 (2.8×10^5-3.32×10^6U/kg) is required for ACT of LAK cells in cancer treatment. Moreover, IL-2 induced serious side effects such as capillary leak syndrome (CLS) or vascular leakage syndrome (VLS) [10,11]. Further studies showed that LAK cells did not prove effective in the treatment of metastatic melanoma and renal cancer patients [12]. In addition, clinical trials discovered that IL-2 administration alone could induce tumor regression in 20% of patients with metastatic melanoma and renal cancer [12]. Therefore, ACT with LAK cells is currently not used in cancer treatment.

CYTOKINE-INDUCED KILLER (CIK) CELLS

CIK cells are also activated PBMC after *in vitro* stimulation by multiple factors including interferon-γ (IFN-γ), IL-1α, IL-2 and anti-CD3 antibody for 7-14 days [13]. They are mainly $CD3^+CD56^+$ cells, i. e. NK cell-like T cells. Similar to LAK cells, CIK cells can kill

varieties of tumor cells *in vitro* and *in vivo* mouse models [13,14]. Nowadays, autologous CIK cells have been extensively used in treatment of cancer patients in China although the effectiveness and mechanisms of ACT with CIK cells are still uncertain [15-18].

Due to the lack of tumor antigen specificities of CIK cells and strong capability of antigen presentation of dendritic cells (DC), DC-CIK cells were recently developed for ACT for cancer. Usually, DCs from peripheral blood samples were pulsed by tumor antigens, tumor lysate or antigen-loaded viral vectors and then co-cultured with CIK cells to grow DC-CIK cells. Compared with CIK cells alone, DC-CIK cells have increased proliferation ability, cytokine secretion and anti-tumor activity [19,20]. Therefore, it is believed that DC-CIK cells are more effective than CIK cells alone in ACT for cancer patients. A clinical trial showed that ACT with tumor lysate-pulsed DC-CIK cells could significantly increase overall survival rates than no treatment control in renal cancer carcinoma patients; however, there was no difference between ACT with DC-CIK cells and IFN-α administration ($P > 0.05$) [21]. Thus, the efficacy of ACT with DC-CIK cells in cancer treatment remains to be determined.

TUMOR-INFILTRATING LYMPHOCYTES (TILS)

It has been documented that TILs could be easily generated from metastatic melanoma patients [22,23]. After expansion, TILs have anti-tumor activity against autologous tumor cells and other cancer cells [22,23]. Clinical trials have demonstrated that ACT with anti-tumor TILs can induce tumor regression in 49-72% of the treated patients with metastatic melanoma [3,24], suggesting that ACT with anti-tumor TILs is an effective method in cancer treatment.

Our studies discovered that the persistence of multiple anti-tumor T cell clones was responsible for tumor regression in metastatic melanoma patients after ACT of anti-tumor TILs [25,26]. We subsequently demonstrated that the telomere length of transferred lymphocytes was associated with T cell persistence and clinical response in patients with metastatic melanoma after ACT [27,28], suggesting that less-proliferated young TILs would be more effective for ACT [29,30]. Thus, telomere length may be used as a marker to select TILs for ACT in order to improve the efficacy of ACT with anti-tumor TILs for cancer patients.

GENETICALLY ENGINEERED LYMPHOCYTES

As mentioned above, ACT of anti-tumor TILs is an effective method for patients with metastatic melanoma. Anti-tumor tumor-infiltrated lymphocytes, however, may not be generated from all cancer patients. Thus, genetically-engineered T lymphocytes with anti-tumor activity are pursued for ACT for cancer [31]. Usually, viral vectors carrying genes coding T-cell receptor genes specific to tumor antigens or chimeric antigen receptors (CARs) are genetically introduced into PBMC or tumor-infiltrating lymphocytes [30,32,33]. Such genetically-engineered T lymphocytes have high avidity and tumor reactivity [34], which may be used for ACT in cancer treatment. For instance, genetically-engineered T lymphocytes are highly reactive to MART-1 melanoma tumor antigen [35]. In addition, infusion of CD19-specific CAR-transduced mouse T cells alone could induce long-term B cell eradication in mouse model of B cell acute lymphoblastic leukemia (B-ALL) [36] and primary human pre-B-cell acute lymphoblastic leukemia [33].

A clinical trial indicated that genetically-engineered T lymphocytes reactive to MART-1 for ACT might be effective in tumor regression in metastatic melanoma patients [4]. Genetically-engineered T lymphocytes reactive to NY-ESO-1 also successfully induced tumor regression in both melanoma patients and nonmelanoma synovial cell sarcoma patients [37]. Furthermore, infusion of genetically-engineered T cells with CD19-specific CARs caused rapid tumor regression in patients with relapsed/refractory B-ALL [38] and advanced chronic lymphocytic leukemia (CLL) [39]. Thus, genetically-engineered T lymphocytes with anti-tumor reactivities may be used in ACT for cancer patients, from whom anti-tumor tumor-infiltrating lymphocytes cannot be generated for therapy.

PROSPECTS IN ADOPTIVE CELL TRANSFER THERAPY

Thus far, there is no evidence available to confirm that ACT of CIK cells and DC-CIK cells is effective in cancer treatment. However, it may be effective when ACT of CIK cells and DC-CIK cells is used together with conventional cancer treatment methods. For instance, ACT with CIK cells in combination with chemotherapy had potential benefits including longer progression-free survival and overall survival in patients with advanced gastric cancer and non-small-cell lung cancer as compared with chemotherapy alone [40,41]. The combination of high-dose chemotherapy with ACT of DC-CIK cells showed clinical benefits such as improved progression-free survival and overall survival in metastatic breast cancer patients [38]. ACT of DC-CIK cells in combination with chemotherapy also could significantly increase the 1- and 2-year overall survival rates in patients with advanced non-small-cell lung cancer [42]. Therefore, ACT of CIK cells and DC-CIK cells in combination with conventional cancer treatments such as chemotherapy may be used as effective treatment modalities for cancer patients.

ACT of anti-tumor TILs has been shown to be effective in the treatment of patients with metastatic melanoma [3]. TILs can also be generated from patients with breast cancer [43], renal cancer [44], pancreatic cancer [45] and lung cancer [23]. These lymphocytes have anti-tumor activity against autologous tumor cells and other cancer cells [23,43,45]. Therefore, ACT using anti-tumor TILs is a promising effective treatment for patients with breast cancer, renal cancer, etc.

Genetically-engineered T lymphocytes with anti-tumor activity against MART-1 seem to be effective in ACT for metastatic melanoma patients [4]. It is possible that genetically-engineered T lymphocytes with anti-tumor activities against other tumor antigens may be effectively used in ACT for other forms of cancer [37]. It is desirable to establish a bank of genetically-engineered T lymphocytes with anti-tumor reactivities against all known tumor antigens. It will facilitate future applications of ACT as an effective treatment for cancer patients as long as specific tumor antigens are identified. For a similar reason, it is worthwhile to establish a bank of anti-tumor TILs from different cancer patients for future ACT in cancer treatment.

In vitro generation of anti-tumor TILs is critical for successful ACT in cancer treatment. The flexibility in manipulations of T cells *in vitro* would overcome tumor-induced T-cell anergy *in vivo* to generate optimal anti-tumor immunity. Anti-tumor TILs may used in the identification of antigens involved in tumor regression mediated by transferred anti-tumor lymphocytes [25,46]. Understanding of antigen specificities in anti-tumor TILs for ACT will have great implications in exploring the mechanism of tumor regression induced by transferred T cells and improving the efficacy of ACT in cancer treatment [25,47]. Furthermore, identification of antigen specificities in anti-tumor TILs would facilitate the generation of genetically-engineered T lymphocytes with anti-tumor activities against specific tumor antigens for ACT.

CTLA-4 (cytotoxic T-lymphocyte antigen-4) interacting with its ligands (B7.1 and B7.2) down-regulates the immune system and thus antibodies that block the interaction between CTLA-4 and its ligands can increase immune responses. Recent studies have shown that monoclonal antibody therapy using anti-CTLA-4, PD-1 (programmed death-1) and CD137 (4-1BB) monoclonal antibodies can enhance immune responses, including anti-tumor immunity [48]. Clinical trials in metastatic melanoma patients demonstrated that antibody therapy with anti-CTLA-4 antibodies (lpilimumab and tremelimumab) could induce melanoma regression and/or improve overall patient survival although serious side effects were found in 10-25% of patients [49-51]. NY-ESO-1 and gp100 vaccination in combination with anti-CTLA-4 antibody therapy increased the vaccine-primed antigen-specific T-cell response in metastatic melanoma patients [51,52]. Therefore, ACT in combination with antibody therapy may provide a promising strategy for improved ACT efficacy in cancer treatment.

ACKNOWLEDGEMENT

This work was supported by “Taishan Scholar” Special Fund (No. 109, 2012) from Shandong Government, China.

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Cite this article

Li Y, Huang Q, Zhong Y, Wang A, Sun J, et al. (2013) Prospects in Adoptive Cell Transfer Therapy for Cancer. J Immunol Clin Res 1: 1008.