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Adoptive cellular immunotherapy for the treatment of patients with breast cancer: A meta-analysis

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Abstract

Background. To evaluate the therapeutic efficacy of dendritic cells (DC) alone, cytokine-induced killer (CIK) cells alone and the combination of DC and CIK cells in the treatment of breast cancer, we performed a systemic review of the relevant published clinical studies, collectively referred to as DC-CIK cell therapy. *Methods.* Six hundred thirty-three patients with breast cancer were assigned to cohorts, and a meta-analysis was conducted. *Results.* The treatment of breast cancer with DC-CIK cells was associated with a significantly improved 1-year survival ($P = 0.0001$). The Karnofsky performance status scale of the patients treated with DC-CIK cells was significantly improved compared with that of the non-DC-CIK group ($P < 0.0001$). The percentage of T cells ($CD3^+$, $CD4^+$ and $CD4^+CD8^+$), $CD16^+$ monocytes, and $CD3^+CD56^+$ natural killer T cells in the peripheral blood of cancer patients was significantly increased ($P \leq 0.05$), whereas the percentage of $CD4^+CD25^+$ regulatory T cells was not significantly decreased ($P = 0.32$) in the DC-CIK treatment group compared with the non-DC-CIK group. 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, which reflect immune function, were significantly increased ($P < 0.001$) after DC-CIK cell treatment. Furthermore, after DC-CIK treatment, the average levels of the alpha-fetoprotein, cancer antigen embryonic antigen and carbohydrate antigen tumor markers were decreased ($P < 0.00001$). *Conclusions.* DC-CIK cell therapy markedly prolongs survival time, enhances immune function, and improves the efficacy of the treatment of breast cancer patients.

Key Words: *breast cancer, cytokine-induced killer cells, dendritic cells, immunotherapy, meta-analysis*

Introduction

Breast cancer is the most common female cancer and was responsible for approximately 1.15 million new cases and 411,000 deaths worldwide in 2002 (1). The disease can usually affect women of all ages. During the past decade, the survival rate for breast cancer patients has increased markedly due to earlier detection and more effective treatment approaches. However, many patients with advanced malignant disease cannot be cured by standard forms of cancer therapy. It is known that surgery, radiation, and chemotherapy have varied side effects and often fail to remove the tumor completely (2). The immune system is increasingly being considered in the fight against tumors. Immunotherapy is a promising treatment option and considered the fourth-line cancer therapy (3,4). Attention is therefore rapidly turning to the use of adoptive cellular immunotherapy for the treatment of breast cancer. Since the potential of immunotherapy was identified, several subsets of immunologic effector cells, such as lymphokine-activated killer cells, tumor-infiltrating lymphocytes, anti-CD3-induced activated killer cells, and γδ T cells, have been used in immunotherapy (3–5). At present, the common immune effector cells applied in immunotherapy are cytokine-induced killer (CIK) cells and dendritic cells (DCs).

DCs constitute a unique subset of extremely efficient antigen-presenting cells (APCs) that were first described in 1973 by Steinman and Cohn (6). Steinman received the 2011 Nobel Prize in Physiology or Medicine for the discovery of DCs and their role in adaptive immunity. The study of DCs has reached an important milestone with the recent approval of Provenge, the first DC-based vaccine

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for the treatment of prostate cancer. Although this heralds a new era of tumor immunotherapy, it also highlights the compelling need to optimize DC-based therapies as they are increasingly tested and used to treat human patients. DCs have the unique ability to process and present peptide fragments on their major histocompatibility complex (MHC) class I and II molecules through a process known as cross-presentation (7). After maturation, DCs migrate to the draining lymph nodes, where they interact with naive T cells to initiate T-cell differentiation toward the Th1, Th2, or Th17 phenotypes. Several factors determine the direction of T-cell polarization and thereby regulate the T-cell response. Interleukin (IL)-12 plays a central role in the immune system not only by augmenting the cytotoxic activity of T cells and natural killer (NK) cells and regulating interferon-γ (IFN-γ) production but also by promoting the development of Th1 cells. These discoveries have resulted in the ability to manipulate immune responses and direct them in specific ways.

CIK cells are non-MHC-restricted $CD3^+CD56^+$ T cells. These cells were first described by Schmidt Wolf *et al.* to have a marked ability to proliferate and an increased cytolytic activity against cancer compared with lymphokine-activated killer cells (8). These cells are generated *in vitro* through the cultivation of peripheral blood lymphocytes with anti-CD3 monoclonal antibody, IL-2, IL-1α, and IFN-γ. CIK cells exhibit both the powerful anti-tumor effect of T cells and the non-MHC restriction of NK cells and are usually called NKT cells. Mature differentiated $CD8^+$ T cells and some types of $CD4^+$ T cells release IFN-γ and tumor necrosis factor (TNF), which enhance the immune response by upregulating the expression of MHC class I and II molecules on both tumor cells and tumor-resident APCs (9). $CD4^+$ T cells are capable of activating and regulating many aspects of innate and adaptive immunity, including the function of cytotoxic $CD8^+$ T cells. They can also engage and "license" APCs, which in turn recruit additional T cells and promote the activation of the innate immune system.

Treatment with autologous and allogeneic DCs and CIKs has shown encouraging clinical prospects for many types of cancer, such as renal cancer, liver cancer, breast cancer, and melanoma (10–13). The first clinical trial using CIK cell therapy for cancer patients was reported in 1999. Soon after, CIK and DC-CIK cells demonstrated encouraging results in several clinical trials. For example, HER2/neu (E75)-, Muc-1- and p53-peptide-pulsed DCs can prevent recurrence and are safe (i.e., not associated with significant toxicity) in high-risk breast cancer patients (12,14,15). These trial studies showed that cancer immunotherapy with DC-CIK cells may prevent recurrence, prolong life, and improve quality of life of cancer patients and thus present a good curative effect. However, clinical studies on DC-CIK cells are still in their infancy, and there is no clear consensus regarding how they may best be optimized. Therefore, we performed a systematic review and meta-analysis of the clinical trials that have been performed to assess the efficacy and tolerability of DC-CIK cells in the treatment of patients with breast cancer. The aim of this review was to evaluate the impact of DC-CIK-based therapy on the survival, clinical response and clinical observation results and to assess the toxicity of this treatment.

Methods

Study design and search strategy

The trials analyzed in this study were identified through an electronic search of the PubMed database, the Cochrane Central Registry of Controlled Trials, the Wanfang Database, the China Science and Technology Periodical Database, China Journal Net, reference lists of published trials, and relevant review articles. The search strategy included the medical subject headings "breast carcinoma," "cytokine-induced killer cells," "dendritic cells" and free text search. No language limits were applied. The initial search was performed on August 2012 and updated in July 2013. Furthermore, we contacted drug manufacturers, asked experts in the field and performed manual searches in reference lists and conference proceedings of the American Society of Clinical Oncology Annual Meetings and the European Cancer Conference. We excluded abstracts that were never subsequently published as full articles and studies on animals and cell lines.

Patients and eligibility criteria

The main criteria for patient inclusion in the trials were the following: (i) histologically proven metastatic or locally advanced breast cancer, (ii) progressive disease and no standard systemic treatment indicated, (iii) World Health Organization performance status 0–2 and (iv) life expectancy of >3 months. The main exclusion criteria included (i) radiation therapy or chemotherapy within the previous 4 weeks, (ii) other malignancies and (iii) pregnancy.

Data collection

We collected various sets of information, including the authors' names, journal and year of publication, sample size per arm, regimen used, median or mean age of the patients and characteristics of the study design (i.e., whether the trial reported the mode of randomization, allocation concealment, description of withdrawals per arm and blinding) for all of the trials included in the study.