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Effectiveness and safety of chemotherapy combined with cytokine-induced killer cell /dendritic cell–cytokine-induced killer cell therapy for treatment of gastric cancer in China: A systematic review and meta-analysis

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Abstract

Background. Currently, cytokine-induced killer cells (CIK)/dendritic cell (DC)-CIK-mediated immunotherapy is widely used to treat gastric cancer. However, limited information regarding clinical trials on CIK/DC-CIK therapy is available. Therefore, systemic evaluation of the efficacy and safety of the combination therapy is necessary. *Methods.* A meta-analysis involving 1735 patients with gastric cancer was conducted. Before analysis, the study quality and heterogeneity were evaluated. The effects of chemotherapy combined with CIK/DC-CIK on gastric cancer were compared with the effects observed when chemotherapy alone was used. Pooled analysis was performed using RevMan version 5.2 from random or fixed-effect models. *Results.* Seventeen trials were included. First, the analysis showed that the combination therapy significantly increased the overall survival rate and disease-free survival rate compared with those in patients treated using chemotherapy alone. The overall response rate ($P = 0.002$), disease control rate ($P = 0.0007$), and quality of life improved rate ($P = 0.0008$) were significantly improved in patients who received combined treatment than in patients who received chemotherapy alone. Second, the percentage of lymphocyte subsets ($CD3^+$, $CD4^+$ and $CD3^-CD56^+$, $CD3^+CD56^+$; $P < 0.01$) and the levels of interleukin-12 and interferon-γ, which reflect immune function, were significantly increased ($P < 0.05$) after the CIK/DC-CIK therapy. Further, carbohydrate antigen tumor markers were significantly reduced compared with the pre-therapy levels. Immunotherapy with CIK/DC-CIK obviously alleviated the adverse events caused by chemotherapy. *Conclusion.* The combination of CIK/DC-CIK therapy and chemotherapy was superior in prolonging the survival time, enhancing immune function and alleviating the adverse events caused by chemotherapy.

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

Introduction

Gastric cancer was considered as the third leading cause of cancer-related deaths according to World Cancer Report 2014, and it caused 723,000 deaths worldwide in 2012 [1]. China is a high-risk area for gastric cancer, and the new cases of gastric cancer in this region account for about 42.5% of cancer cases in the world [2]. Studies suggest that the causes of gastric cancer are related to eating habits, genetic factors, stomach diseases and other factors [3]. In recent years, several young people have been diagnosed with gastric cancer and patient numbers have doubled over the past 30 years [2]. Early gastric cancer is easily misdiagnosed owing to the fewer symptoms. In most affected patients, gastric cancer progressed to the advanced stage or metastasized, and the 5-year survival rate was <20% at this stage [4]. Currently, surgery, radiotherapy and chemotherapy are the three most widely used cancer treatments. However, these treatments often fail to completely remove the tumor tissues, including small lesions and metastatic cells that may cause disease recurrence after treatment. Moreover, drug resistance and the multiple subsequent

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adverse effects make these treatments even more difficult [5,6]. Thus, more effective and safer treatments are urgently required.

In recent years, the rapid development of cancer immunotherapy, such as tumor-infiltrating lymphocytes (TILs) [7], natural killer (NK) cells [8], cytotoxic T-lymphocytes (CTLs) [9], cytokine-induced killer cells (CIKs) [10] and other immune cells, provides a new approach for cancer treatment, considered as fourth-line cancer therapy [11,12]. CIKs or dendritic cells (DCs) combined with CIKs (DC-CIK) has attracted increasing attention as an effective cellular immunotherapy [13–16]. Compared with other immune cells, CIKs exhibit a higher proliferation rate, stronger antitumor activity and broader anti-tumor spectrum [17]. CIKs, which are cytotoxic lymphocytes generated by incubation of peripheral lymphocytes with anti-CD3 monoclonal antibody, interferon (IFN)-γ and interleukin (IL)-2, mainly consist of the $CD3^+CD56^+$ subset. These cells exhibit both the powerful anti-tumor effect of T cells and the non-MHC (Major histocompatibility complex) restriction of NK cells [18–20]. They cause less toxicity to normal bone marrow hematopoietic progenitor cells, and the killing activity of the CIKs is not affected by immune inhibitors such as CsA (Cyclosporin A) and FK506 (Tacrolimus) [21]. CIKs induce tumor cell apoptosis and kill them through direct contact, and secrete cytokines such as IL-2 and IFN-γ [22]. DCs are the most potent antigen-presenting cells in the body, presenting tumor antigens to T lymphocytes and inducing anti-tumor immune responses [23,24]. They also act as stimulators of effector T cells, promoting the generation of helper and cytotoxic T cells [25]. Further, DCs can promote the gathering of effector T cells around the tumor site and the pathogenic tissue by secretion of chemokines [26]. The combination of DCs and CIKs leads to a remarkable increase in cytotoxic activity [16]. Several studies have indicated that both CIKs and DC-CIK were effective in treating multiple solid tumors including non-small cell lung, breast, colon and other cancers, without any serious adverse reactions [13–16].

Studies have shown that CIK/DC-CIK combined with different chemotherapy regimens for treatment of gastric cancer shows better efficacy than that shown by treatment with chemotherapy alone (Table I). However, clinical studies on cellular immunotherapy with CIK/DC-CIK cells are still in their infancy. Therefore, we performed a systematic review and meta-analysis of the clinical trials that have been performed to assess the efficacy and tolerability of CIK/DC-CIK cells combined with chemotherapy for treatment of patients with gastric cancer. This review aimed to evaluate the impact of combination therapy on patient survival, clinical responses, safety and immune functions.

Materials and methods

Search strategy and selection criteria

The trials analyzed in this study were identified through an electronic search of the Cochrane Library, and the PubMed, Wanfang and CNKI databases (Chinese National Knowledge Infrastructure). The search terms were "dendritic cells," "immunotherapy," "cytokine-induced killer cells" or "DC-CIK" combined with "gastric cancer." There were no language and date restrictions in the selection of studies. The initial search was performed in January 2015 and updated in December 2015. We also requested more clinical information from drug manufacturers. Our search was based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [27].

The selection criteria for this study were as follows: (i) trials were eligible for the present meta-analysis if they were randomized controlled trials of patients with gastric cancer; and (ii) patients in the experimental group received chemotherapy combined with CIK or DC-CIK immunotherapy, whereas patients in the control group were treated using chemotherapy alone.

Data collection and quality assessment

Data was extracted independently by two reviewers, and any disagreements were discussed with a third investigator. The following data were collected: the first author's name; the year of publication; tumor stage; experiment regimens; chemotherapy regimens; number of subjects; patient age; culture conditions; and dose of immune cells.

The quality of the included studies was assessed based on the Cochrane Handbook by recording seven bias risks, namely, random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data addressed, and free of selective reporting. Each of the six items was scored as "low risk," "unclear risk" or "high risk" [28].

Curative effect evaluation

Clinical responses were assessed in terms of the overall survival (OS) and disease-free survival (DFS) to evaluate prognosis, and treatment efficacy was assessed in terms of the overall response rate (ORR), disease control rate (DCR) and quality of life improved rate (QIR). OS was defined as the time from the initiation of treatment until death from any cause. DFS was defined as the length of time from the initiation of treatment to the first evidence of recurrence or death. ORR was defined as the sum of complete and partial response rates, and DCR was the sum of complete response, partial response and stable disease rates. QIR was defined as the improvement in quality of life after treatment [29].