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Effect of dendritic cell–based immunotherapy on hepatocellular carcinoma: A systematic review and meta-analysis

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Abstract

Background aims: Dendritic cell (DC)-based immunotherapy has recently been reported frequently in the treatment of hepatocellular carcinoma (HCC); however, its efficacy remains controversial. In this study, we aimed to evaluate the clinical efficacy of DC-based immunotherapy on HCC by conducting a systematic review and meta-analysis. *Methods:* PubMed, Cochrane Library, Embase and Web of Science were searched to identify clinical trials on DC-based immunotherapy for HCC published up to January 31, 2018. The articles were selected according to pre-established inclusion criteria and methodologic quality, and publication bias were evaluated. *Results:* A total of 1276 cases from 19 clinical trials were included. Compared with traditional treatment, further DC-based therapy enhanced the $CD4^+$ T/$CD8^+$ T ratio (standardized mean difference: 0.68, 95% confidence interval [CI] 0.46–0.89, $P < 0.001$); increased the 1-year, 18-month and 5-year progression-free survival (PFS) rate and the 1-year, 18-month and 2-year overall survival (OS) rate (relative risk > 1, $P < 0.05$), prolonged the median PFS time (median survival ratio [MSR]: 1.98, 95% CI: 1.60–2.46, $P < 0.001$) and median OS time (MSR: 1.72, 95% CI: 1.51–1.96, $P < 0.001$). Adverse reactions were mild. *Conclusions:* DC-based therapy not only enhanced anti-tumor immunity, improved the survival rate and prolonged the survival time of HCC patients, but it was also safe. These findings will provide encouraging information for further development of DC-based immunotherapy as an adjuvant treatment for HCC. However, the results must be interpreted with caution because of the small study numbers, publication bias and the various of study designs, pre-treatment and therapeutic processes of DCs.

Key Words: *DC-CIK, dendritic cell vaccine, hepatocellular carcinoma, immunotherapy, meta-analysis*

Introduction

According to the 2014 World Cancer Report, hepatocellular carcinoma (HCC) represents the fifth most common cancer worldwide with 782 000 new cases per year; the incidence is higher in males than females. HCC is also the second largest cause of cancer-related death. Given the high fatality in liver cancer patients (overall mortality-to-incidence ratio of 0.95) and that there were approximately 746 000 HCC-related deaths in 2012, this type of cancer represents a significant health burden globally [1]. The major risk factors of HCC occur in the setting of chronic viral hepatitis, alcohol abuse, and nonalcoholic steatohepatitis. Most of the burden of HCC (85%) is borne in developing countries, especially in East and Southeast Asia and sub-Saharan Africa, which have the highest incidence rates and where hepatitis B virus (HBV) is endemic [2]. HCC progresses quickly and presents a poor prognosis. Early-stage tumors are always dealt with surgically (resection or liver transplantation) or with local therapies including radiofrequency ablation (RFA), percutaneous ethanol injection, percutaneous microwave coagulation therapy and cryotherapy [3]. Another major problem is that only 30% of patients are eligible

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for the aforementioned treatments because HCC frequently remains undiagnosed until the cancer has reached an advanced stage. The main treatment methods for intermediate- and advanced-stage tumors include, for example, transcatheter arterial chemoembolization (TACE), radiation therapy, chemotherapy and molecular targeted therapy [3]. Multi-targeted tyrosine kinase inhibitor drugs, such as sorafenib and regorafenib, can significantly prolong survival time in advanced HCC patients [4,5]. Even after these treatments, the 5-year survival rate of HCC is still low—only 26% in the United States. The main obstacle to improving the post-treatment prognosis of HCC is a high recurrence rate [6]. Therefore, development of a new effective strategy to suppress the recurrence of HCC is necessary, and immunotherapy may have broad applications in this area.

The journal *Science* rated immunotherapy as the top scientific breakthrough in 2013 [7]. There are many immunotherapeutic approaches for HCC, including adoptive immunotherapy, immune checkpoint inhibitor and dendritic cell (DC) vaccine, among others [8]. DCs were first discovered by Steinman in 1973, who won the 2011 Nobel Prize in Physiology and Medicine [9]. DCs are the most powerful type of professional antigen-presenting cells and play a key role in primary immune responses, tolerance and maintenance of immune homeostasis. Additionally, DCs act as an important bridge between the innate and adaptive immune system. DCs can help immunocytes improve their cytotoxicity, due to a large number of dendrites, to numerous types of surface molecules and receptors and to secreted cytokines [10,11]. Studies have shown that impaired DC function may be an important factor in immune escape of HCC [12]. DC-based therapy is designed to raise the specific immune response against existing tumor cells. DC-based therapy can improve the cytotoxic effect on HCC cells and has also achieved good results in animal experiments [13]. In view of this, scientists have conducted a number of clinical trials with DCs.

The preparation process of DC vaccines is generally similar among studies. First, separate peripheral blood mononuclear cells from patients' peripheral blood. Then the adherent cells are cultured into DCs under the induction of cytokines such as granulocyte-macrophage colony-stimulating factor, interleukin (IL)-4 and tumor necrosis factor-α; non-adherent cells were induced into cytokine-induced killer cells (CIK) in the presence of interferon (IFN)-γ, CD3 antibody, IL-1α and IL-2. Second, DCs are pulsed with the patient's whole HCC cell antigens, such as tumor lysates or tumor-associated antigens (TAA). Third, DC vaccine is injected into the patient.

The purpose of this article is to summarize the published clinical trials on DC-based therapy in the treatment of HCC using the method of meta-analysis to evaluate the therapeutic effect of DC-based therapy on HCC and to provide a valuable guidance in HCC immunotherapy.

Methods

Literature search

Two authors independently searched the PubMed, Cochrane Library, Embase and Web of Science Core Collection databases for relevant articles published from established to January 31, 2018. No language restriction was imposed. Search terms included "hepatocellular carcinoma," "dendritic cell," "vaccine," "DC-CIK," "immunotherapy" and "clinical trial." The search strategy was combined with subject words (MeSH, Emtree) and free words. In addition, the reference lists of identified studies were checked manually to include other potential eligible trials.

Inclusion criteria

Population: Consistent with the diagnostic criteria of HCC, patients were diagnosed from histopathology, imaging, and α-fetoprotein serum concentration combined with clinical symptoms and signs [3], regardless of geographic area, race, age or gender.

Intervention: Experimental groups comprised primary HCC patients who accepted DC vaccine or DC-CIK immunotherapy, including those who were post-surgery, post-treatment or advanced patients who could not tolerate routine treatment.

Comparison: Control groups comprised those who would not accept DC vaccine or DC-CIK.

The outcome of interest was the data on immunological changes and clinical indexes from clinical trials, including randomized controlled trials (RCTs) and non-RCTs.

Data extraction and quality assessment

Two authors (C.C. and Y-H.M.) independently selected the articles and extracted the data; if there were any differences, a third researcher (Y-T.Z.) was invited to discuss. The following data were extracted: first author, year of publication, number of patients, patient characteristics, intervention methods (experimental and control groups, injection route), outcomes ($CD4^+$ T/$CD8^+$ T ratio, progression free survival [PFS] rate, overall survival [OS] rate, median PFS time and median OS time), adverse events, study type and quality score. Extracted data were entered into a standardized Excel file. The methodological quality of RCTs was evaluated by