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A comparison of clinical outcomes between radiotherapy and autoimmune cells therapy in non-small cell lung cancer patients

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ABSTRACT

Purpose: This study aimed to compare the clinical outcomes of immunotherapy with dendritic cell (DC) vaccine and cytokine-induced killer (CIK) cells with those of radiotherapy in non-small cell lung cancer (NSCLC).
Methods: The immunotherapy group included 197 NSCLC patients with stage IIIb–IV disease, loco-regional recurrence, or distant metastasis after surgery who received immunotherapy with DC vaccine and CIK cells. Delayed type hypersensitivity (DTH) skin test results, quality of life (QOL), and safety were analyzed. The well-balanced control group included 192 patients receiving radiotherapy. All patients were followed-up for 569.87 ± 295.52 days for overall survival (OS) analysis using the Kaplan-Meier method.
Results: DTH results, QOL, and side effects data were available for 197 patients in the immunotherapy group. One hundred and twenty-one of these (61.42%) developed a positive immune response to immunotherapy evidenced by the DTH skin test, and 180 (91.37%) had improved QOL. Fever was observed in 67 patients (34.01%), insomnia in 86 (43.65%), anorexia in 71(36.04%), joint soreness in 33 (16.75%), and skin rash in seven (3.55%). No server toxicities were observed in the immunotherapy group. Compared with the control group, OS was significantly prolonged in the immunotherapy group (P=0.000). OS rates at 6, 12, and 18 months were 88.8%, 82.2%, and 79.6% in the immunotherapy group and 73.4%, 64.1%, and59.3% in the control group, respectively.
Conclusions: Immunotherapy with DC vaccine and CIK cells might induce an immune response against NSCLC, improve QOL, and offer a survival benefit without severe toxicity in NSCLC patients, compared to radiotherapy.

1. Introduction

Lung cancer is the most common cause of death from cancer malignancy in the world. Among them, non-small cell lung cancer (NSCLC) accounts for about 80% of all cases [1]. Surgery, radiotherapy, and chemotherapy remain the standard therapeutic options for NSCLC patients [2]. However, most of them are not suitable for surgery because they are often diagnosed at an advanced stage (stage IIIb or IV) [3,4]. Furthermore, patients undergoing radical surgery might eventually develop loco-regional recurrence or distant metastasis [5,6]. Advanced NSCLC is highly malignant and characterized by inexorable disease progression. Its prognosis is poor, despite chemotherapy and/or radiation. Although systemic chemotherapy is recommended as the first-line treatment for patients with advanced stage and metastatic NSCLC, it is often considered ineffective or excessively toxic [7,8]. Therefore, new treatment modalities for NSCLC are urgently needed, and immunotherapy has been developed as a potential option [9]. Additionally, multidisciplinary therapy is generally accepted as a possibility for the treatment of advanced NSCLC [10].

Immunotherapy has been suggested as an important and efficient therapeutic option for cancer patients, especially those with late-stage disease [11]. Immune response cells such as cytokine-induced killer (CIK) cells and dendritic cells (DC) might participate in the development of an effective immune response against cancer cells and help eliminate them [12–14]. The combination of conventional treatment such as surgery, chemotherapy, and radiotherapy with immunotherapy might be a novel approach to anti-cancer therapy for the ultimate goal of reducing mortality [2,15].

In the present study, we evaluated the immune response induced by immunotherapy with DC vaccine and CIK cells in advanced NSCLC patients. Improvements in patients' quality of life (QOL) and treatment-related side effects were also assessed. Furthermore, the overall

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survival (OS) of patients receiving immunotherapy or radiotherapy (the control group) was compared to analyse the potential survival benefit from DC vaccine and CIK cells in advanced NSCLC.

2. Patients and methods

2.1. Study design

The present investigation was a retrospective clinical study finished at the Department of Oncology, Tianjin Union Medicine Centre, Tianjin, China. All patients were referred to our department between January 4, 2012 and June 30, 2013. The study protocol was approved by our institutional ethics committees, and class III medical techniques of "Treatment with autologous immune cells (T cells or NK cells)" were performed in accordance with the Minister of Health of China policy. All patients provided written informed consent before receiving treatment.

2.2. Patients

Inclusion criteria were as follows: (1) hospitalization for immunotherapy with DC vaccine and CIK cells for NSCLC between January 4, 2012 and June 30, 2013; (2) unresectable NSCLC and loco-regional recurrence or distant metastasis after surgery; and (3) adequate function of the kidneys, liver, coagulation, and bone marrow. (4) Patients wth chemotherapy (if any) of TP regimen were included (T: paclitaxel or docetaxel; P: cisplatin or carboplatin). Patients who met these criteria were enrolled as the immunotherapy group, whereas the control group included patients receiving radiotherapy who had well-balanced characteristics compared to those in the immunotherapy group.

2.3. Preparation of immunocytes

Immunocytes, including DCs and CIK cells, were prepared as previously described [16–18]. The Fresenius KABI System was used to collect the peripheral blood mononuclear cells (PBMCs) through a process of leukapheresis. Then, PBMCs were cultured with serum-free medium overnight. Adherent cells (consisting of monocytes) and non-adherent cells (consisting of lymphocytes) were then separated. Scine only 15.93% patients (62/389) underwent primary tumor resection, the autologous tumor lysates could not be gtten. Two lung cancer cell lines, SPC-A-1 for adenocarcinoma and SK-MES-1 for squamous cell carcinoma, were cultured for 24 h at 37 °C, ultrasonicated, and centrifuged at 600g for 30 min. Tumour lysate was obtained by collecting the supernatant and used for pulsing DCs and delayed type hypersensitivity (DTH) testing.

Under the activating with granulocyte-macrophage colony-stimulating factor, interleukin (IL) 4, tumour lysate,and tumour necrosis factor for 7 days, DC vaccine was prepared by culturing the adherent cells [19,20]. CIK cells were prepared by culturing the non-adherent cells in the presence of interferon gamma, CD3 monoclonal antibody, and IL-2 for 11 to 14 days [21].

2.4. Quality control of immunocytes

The immune phenotypes were analysed by flow cytometry through expression of HLA2DR, CD80, and CD83 for DCs and CD3, CD8, and CD56 for CIK cells. The cultured samples of DCs and CIK cells were checked to ensure no bacterial or fungal contamination, and the endotoxin levels were less than 5 EU/kg. Intradermal vaccination with DCs was administered using 1×10^7 cells. For intravenous vaccination, DCs were solubilized in 100 ml of normal saline (NS) for intravenous vaccination. CIK cells were infused intravenously using 1×10^9 cells in 100 ml NS. For more detailed information on quality control of immunocytes, please refer to our published papers [17].

2.5. Reinfusion of immunocytes

PBMCs were collected on day 0 of the treatment schedule. Subsequently, 1×10^7 DCs were intravenously infused once a week for 6 weeks starting from day 8, and 1×10^9 CIK cells were intravenously infused once a day for 4days from days 11 to 14.

2.6. DTH

DTH tests were conducted one week after the last DC vaccination by intradermal injection of 4 μg of tumour lysate. After 48 h, the tests were read. Based on the diameter of induration, the results were graded as follows: strongly positive, >10 mm; positive, 5–10 mm; weakly positive, 2–5 mm, and negative, <2 mm [22].

2.7. QOL

The general status of physical strength, appetite, sleeping, and body weight was evaluated as indexes of improved QOL. The number of improved indexes were reported, with 1–4 improved indexes being considered as a progress of patients' general status results [23,24].

2.8. Safety

During the process of immunotherapy, fever, insomnia, anorexia, joint soreness, and skin rash were considered as the side effects [25].

2.9. OS

All patients were followed-up until September 30, 2014. OS was calculated from the date of study enrolment to that of death. Data on patients who were lost to follow-up with an uncertain cause of death or unconfirmed date of death were censored. This definition might result in the number of dead patients to be the same degree of less than the actual in both experimental group and control group.

2.10. OS rates

The OS rates at 6, 12, and 18 months were calculated for both patient groups.

2.11. Data collection and statistical analysis

OS was the primary efficacy end point, meanwhile DTH results, QOL, and safety were the secondary end points for this study. Clinical data were collected from the Inpatient Electronic Medical Records of our hospital, re-analysed, and documented to conform to the aims of this study using Epidata database (version 3.02). All statistical analyses were performed using SPSS (version 19.0, IBM SPSS, Chicago, IL, USA), docked with Epidata database (version 3.02, EpiData Association, Odense, Denmark). OS curves were generated using the Kaplan-Meier method. The P value of less than 0.05 was selected as statistically significant.

3. Results

3.1. Patient characteristics

The study cohort included 389 patients with advanced NSCLC. The patients' mean age was 66.17 ± 10.59 (range, 30–89) years. There were 238 men and 151 women. Tumour burden was observed in 337 patients, including locoregional recurrence in 197 and distant metastasis in 140. The tumor burdern in the other 52 patients were eliminated by chemotherapy before inclusion. The tumour type was adenocarcinoma in 219 patients, squamous cell carcinoma in 145, and undefined in twenty-five. The tumour grade was good in forty-three